The Canadian Medical Association Journal

Vol. 57 SEPTEMBER, 1947 No. 3

THE PATHOLOGICAL ANATOMY AND LETHAL FACTORS IN ACUTE FATAL CRANIO-CEREBRAL INJURY

D. Magner, B.Sc., M.D.*

Regina, Sask.

THE most striking lesions seen at autopsy in cases of acute fatal head injury are lacerations and contusions of the brain. It has not been sufficiently widely recognized that such lesions, even when severe, very frequently cause neither unconsciousness nor death. Hæmorrhages deep in the brain substance, such as sometimes occur in cases of acute cranio-cerebral injury, are equally unlikely to be fatal unless situated in the hypothalamus or floor of the fourth ventricle. On the other hand cerebral compression consequent upon space-occupying intracranial lesions may be considered a valid cause of death, and concussion may be of great importance as a lethal factor.

With a view to examining the factors leading to death, as well as the patterns of bony and cerebral damage, in a representative series of cases of acute head injury, 30 cases from the autopsy files of a special Canadian military hospital, stationed in England, were reviewed. These cases occurred between November 1940 and December 1943. The ages of the patients varied from 20 to 42, the average age being 25 years. The types of accident responsible for the head injury are listed in Table I. The first clinical notes reported 1 patient as fully conscious, 3 as conscious but confused, 5 as irrational or semiconscious and 20 as unconscious. One patient was found dead on the road. The survival time varied from 3 hours to 13 days in the 29 cases in which it could be ascertained.

TABLE I.
TYPES OF ACCIDENT — 30 CASES

Motor cycle crash	8
Motor vehicle crash	6
Hit by motor vehicle	4
Injured in brawl	3
Fall from moving vehicle	2
Fall from bicycle	2
Fall from window	2
Fall down stairs	1
No details	2

SKULL FRACTURE

Twenty-five of the 30 cases showed fracture of the cranial bones. In 21 cases both vault and base were involved, in 1 the vault alone was fractured and in 3 the fracture was confined to the base. The sites of scalp wounds, and sometimes the position and direction of the fracture lines, gave an indication as to where the main violence had been applied. This had been to the frontal region in 10 cases, to the temporo-parietal region in 8 cases, to the occiput in 6 cases and to the vertex in 1 case. Fractures of the vault ran into the base in the cranial fossa nearest to the site of application of violence. In the base fractures of the anterior or middle fossæ tended to remain confined to the thin bone of the central parts of these fossæ, and usually did not breach the thick bony ridges bounding them, but extended in to reach the sphenoid bone. Fractures of the posterior cranial fossa either ran to the foramen magnum or coursed more laterally to the petrous portion of the temporal bone sometimes crossing this.

Comminution was frequent, occurring in 18 cases, usually in the superior orbital plate or the temporal squama. Depression was present in 9 cases, usually in the anterior wall of the frontal sinus, or in the temporal squama. Frontal and ethmoidal sinuses, or middle ears, were opened by the fracture in 17 cases and in 12 of these the sphenoid sinus was also fractured. In 1 the sphenoid sinus alone was involved. Dural tears were noted in 9 cases, but may have been present in a larger number. When reported they were in relationship to comminuted depressed fractures.

* Formerly Lieut.-Col. R.C.A.M.C.
From the Department of Pathology of a special Canadian military hospital, stationed in England.

INTRACRANIAL LESIONS AND CEREBRAL COMPRESSION

Intracranial lesions occurred in 28 of the 30 cases and in 25 cases were associated with skull fracture. In the 2 cases in which gross lesions were absent fracture had not occurred. The lesions encountered were (1) extradural, subdural and subarachnoid hæmorrhages, (2) lacerations and contusions primarily of cerebral surfaces, (3) deep intracerebral hæmorrhages with associated softening. It was of interest that in 3 cases gross intracerebral lesions were present in the absence of skull fracture.

There was autopsy evidence of increased intracranial pressure in 20 cases. Increase in supratentorial pressure was evidenced by flattening, widening and pallor of the cerebral convolutions, and the formation of a so-called tentorial pressure cone by herniation of the central portions of the temporal lobes into the tentorial incisura. This resulted in deep grooving of the hippocampal gyri by the free edges of the tentorium. Frequently the third cranial nerves were distorted or flattened and in one case interference with the blood supply through the left posterior cerebral artery had resulted in cortical infarction. When the increase in supratentorial pressure was predominantly unilateral the tentorial herniation was more marked on that side and the brain stem was displaced to the opposite side. Herniation of cerebellar tonsils into the foramen magnum had occurred in most of these cases but was not extreme.

TABLE II.
CEREBRAL LESIONS ASSOCIATED WITH COMPRESSION OF BRAIN — 21 CASES

Extradural hæmorrhage	4
Subdural hæmorrhage (diffuse)	1
Subdural hæmorrhage ("exploded" pole)	4
Intracranial hæmorrhage (large)	2
Surface lacerations and small intracerebral hæmorrhages	5
Surface lacerations alone	5

Table II shows the cerebral lesions which were associated with evidence of compression. It is evident that large hæmorrhagic lesions take up considerable space and hence cause cerebral compression. Compression associated with the last two types of lesion listed (petechial hæmorrhages in brain and cortical lacerations) was usually of minor degree. In one case definite evidence of compression was present in the absence of gross lesions. The exact mechanism in such cases is a matter of conjecture. Generalized or localized cerebral œdema may be an explanation but often was not demonstrable at autopsy.

EXTRADURAL HÆMORRHAGE

Small quantities of blood clot in the extradural space in relationship to fracture lines were frequent, and were due usually to bleeding from small vessels in the diploe. In one case a small tear in a venous sinus, associated with an occipital fracture had resulted in a small collection of blood in the posterior cranial fossa. Massive extradural hæmorrhage due to fracture of the temporal squama with rupture of a branch of the middle meningeal artery had occurred in 4 cases. In one case the clot had been removed at operation. In the other 3 cases a large solid dark-red disc of clotted blood was adherent to the outer surface of the dura. A saucer-like depression made by the clot was present in the underlying brain. Every case showed signs of cerebral compression, and in one case interference with the vascular supply consequent upon tentorial herniation had resulted in cortical infarction in the distribution of the left posterior cerebral artery. Every case showed surface lacerations of the brain and in 2 cases there were deep intracerebral hæmorrhages, in one case in the brain stem and in the other in the thalamus.

SUBDURAL HÆMORRHAGE

Subdural hæmorrhage in the form of a thin film of blood disposed over the lateral surfaces of the hemispheres occurred in 6 cases. Massive subdural hæmorrhage was present in 6 cases. In one of these violence to the occipital region had failed to cause skull fracture, but massive hæmorrhage into the subdural space, bilaterally, over the vertex, had occurred, presumably from the rupture of large cerebral veins at their entrance into the superior longitudinal sinus. In the other 5 cases the subdural hæmorrhage had a different origin, one stressed by Botterell[1] and by Stewart.[2] In each case severe widespread cerebral laceration, in the contrecoup situation, with tearing of the arachnoid membrane, had resulted in the oozing of blood and pulped brain into the subdural space in the adjacent cranial fossa. This, with œdema of damaged brain, had constituted an expanding lesion in every case, with severe cerebral compression. In each case the violence was oc-

cipital and the laceration was contrecoup. In 2 cases the frontal pole was involved, in 3 the temporal pole. In 4 cases damage was to the side opposite to that on which the violence had been applied.

SURFACE LESIONS

The surface of the brain was damaged in 24 cases. The degree of laceration of the brain varied. Sometimes only cortex was involved. Sometimes there was extension into the deeper portions of the hemisphere with involvement of basal ganglia and internal capsule. In a few instances the laceration had resulted in breaching of the ventricular wall. Lacerations were accompanied by layers of hæmorrhage into the subarachnoid space. In several cases tearing of the arachnoid had caused subdural hæmorrhage as has been described.

Certain surface lesions were related to the depressed comminuted fractures of cranial bones, and were obviously due to direct traumatization. A large number of surface lesions, however, were not attributable to direct trauma. Many of them were of the well-known "contrecoup" variety. Many were situated at the point of application of violence to the head, that is, in the "coup" situation. Lesions of this type, it has been suggested, may be due to the momentary inbending of the skull at the point struck, with or without fracture. Lesions in the contrecoup position, and those neither coup or contrecoup in location, may be due to movements of the brain within the skull. These matters will be discussed further on. Meanwhile, for the sake of simplicity, laceration of the brain not due to direct trauma by depressed fractured bone fragments will be grouped under the term "coup-contrecoup". In 16 cases in the present series they were of this type. In 6 cases they were due to direct trauma, and in 2 cases lesions of both types were present.

In 9 cases the violence was frontal, and the lesions were confined to the frontal and temporal lobes, being in the frontal poles and subfrontal areas in all but 2. In no case was the occipital pole involved. In 5 cases extensive comminution of bone with dural tearing showed that the lesions were due to direct traumatization. In 4 cases a coup-contrecoup mechanism seemed to have been responsible. It will be noted that the lesions were in the coup situation.

In 6 cases the violence was temporal. In one instance direct traumatization by fractured bone had lacerated the lateral surface of the hemisphere. In the other cases the main lesions were of the coup-contrecoup variety and were usually subfrontal and subtemporal. In only 1 case was the laceration truly contrecoup in position, being in the lateral surface of the hemisphere opposite the side struck.

In 2 cases high parietal violence had caused coup-contrecoup lesions in subfrontal and subtemporal regions. In 6 cases the violence was occipital. Of these, 1 case showed a cerebellar laceration and 1 a small occipital laceration, while in the other cases the occipital lobes were spared. All 6 cases showed coup-contrecoup lesions in the frontal and temporal lobes in the polar and inferior surfaces, that is, in the contrecoup situation.

TABLE III.

DISTRIBUTION OF SURFACE LACERATIONS OF BRAIN — 24 CASES

Subfrontal	15
Temporal pole	10
Frontal pole	8
Subtemporal	8
Lateral temporal	4
Lateral frontal	3
Lateral parietal	1
Occipital pole	1
Cerebellum	1

The frequency with which various regions of the brain were affected is shown in Table III. It is of interest that coup-contrecoup lesions due to frontal violence were in the coup situation while lesions of this type due to occipital violence were contrecoup in position. That is, whether the violence was to the front or back of the skull the lesions not due to direct trauma by depressed bone were in the frontal and temporal regions, with sparing of the occipital region. Violence to the sides or top of the skull caused coup-contrecoup lesions in the inferior surfaces of frontal and temporal lobes.

DEEP INTRACEREBRAL LESIONS

This term is used to indicate hæmorrhagic lesions in the substance of the brain not related to lacerations involving the cerebral surfaces. Such lesions take the form of small or larger groups of petechiæ, punctate hæmorrhages measuring up to a few millimetres in diameter, and larger areas of hæmorrhage with associated softening. Fifteen cases showed lesions of this type. In 5 cases they were confined to the hemispheres, in 8 there were lesions in the hemispheres and also in the midbrain or

pons, and in 2 midbrain or pontine hæmorrhages alone were present.

As regards the lesions encountered in the cerebral hemispheres, in 10 of the 13 cases there were petechial or punctate hæmorrhages often diffusely scattered. In 3 cases the hæmorrhages were large. In one of these temporal violence, without skull fracture, had caused subtemporal coup-contrecoup laceration and massive hæmorrhage into the basal ganglia and internal capsule on the side opposite the violence. In the second case occipital violence, with fracture, had caused coup-contrecoup frontal and temporal laceration, and a large hæmorrhage into the right frontal white matter. The third case was one without skull fracture. The sole lesions were a large hæmorrhage into the left putamen, claustrum and external capsule. These 3 cases were all associated immediately and directly with accidental violence. All 3 soldiers were previously well and in the third decade of life. Hence the possibility of antecedent cardiovascular disease being responsible for the cerebral hæmorrhages seems excluded. In no case were congenital "berry" aneurysms of any cerebral artery found. It can be assumed therefore that the deep intracerebral lesions were due to head injury.

Midbrain or pontine lesions were present in 10 cases. In the majority of cases they were described as petechial, punctate or small. In 3 cases they measured over 1 cm. in diameter. Eight of the 10 cases showed more than one hæmorrhagic midbrain or pontine lesion. A small group of focal lesions of varying sizes was the usual finding. In 2 cases petechiæ were noted in the floor of the fourth ventricle and in 1 case in the hypothalamus. In only 2 cases were these hæmorrhages unassociated with hæmorrhagic lesions in the hemispheres. In one of these there was associated cerebral compression due to extradural hæmorrhage, but in the second there was no evidence of cerebral compression.

CAUSES OF DEATH

Most of the cases in this series showed cortical lacerations and contusions. Recent experience with patients suffering from head wounds due to penetrating missiles has confirmed the impression that such lesions, even when severe, if supratentorial, are not of themselves responsible for death or even unconsciousness. It is generally recognized that cerebral compression may cause death due to interference with the hypothalamic autonomic vegetative centres. Midbrain and pontine lesions also may be lethal due to damage to the respiratory and vasomotor centres. A third potent death-producing factor in cases of this type is concussion. (However, since morphological changes in the human brain due to pure concussion have not yet been established, this diagnosis is rarely made.) It must be stressed that in many cases a combination of these factors may be operative.

In 8 cases it is believed that concussion was the main lethal factor. All these were characterized by unconsciousness produced instantaneously at the time of the accident and lasting until death. One case previously reported by Botterell and Wilson[3] showed no cerebral lesions at autopsy. A second case showed only mild cerebral œdema. In 6 additional cases the lesions found at autopsy were judged insufficient to have caused death, and, taking into consideration the clinical course, it seemed that concussion was mainly responsible for the fatal outcome.

As regards compression, it was difficult to evaluate from autopsy records the degree to which this condition was present. It seemed that in 6 cases it was extreme, in 9 moderate and in 4 slight. In 13 cases it was judged to have played a large rôle in producing death, but in 11 of them the element of concussion was present. In 2 cases consciousness was not lost at the time of the accident and it is believed that death was due to pure compression.

In 3 cases extensive pontine hæmorrhages were considered to have been mainly responsible for death. Compression was slight or absent in these cases, but as all were unconscious from the time of injury until death, concussion was probably a factor.

In 2 cases death, although due to head injury, was less immediately related to it. One patient suffered comminuted fractures of the frontal squama and anterior fossæ with involvement of the paranasal sinuses. Pneumococcal meningitis, developing 7 days after the accident, resulted in death 5 days later. At autopsy the fractured sphenoid sinus contained purulent material and had evidently been the source of the meningeal infection. In the second case fracture of the frontal squama and anterior fossæ involved both frontal sinuses. Despite a cerebrospinal fluid leak from the corner of

the left eye the patient, who at no time had been unconscious, did well until 9 days after injury when radiological examination showed a right frontal aerocœle. An immediate operation was done with removal of the aerocœle and softened brain, as well as obliteration of the paranasal sinuses. The procedure went well and the surgeon was closing the incision when the patient died suddenly.

In the remaining 4 cases death was due to causes not directly related to the head injury. One patient died early of multiple injuries, including fracture of the larynx and mediastinal emphysema. Another patient died shortly after injury with fracture of the larynx in which was wedged a portion of aspirated dental plate. A third patient developed bilateral suppurative bronchopneumonia secondary to extensive chest injury with fracture of ribs. One patient was admitted to hospital unconscious, after a motorcycle crash. There was a fracture-dislocation of the right elbow with considerable soft tissue damage. Oliguria developed on the seventh day and death occurred 6 days later with a blood urea of 400 mgm. %. The autopsy revealed a large hæmorrhage into the left putamen and external capsule and punctate hæmorrhages of the corpus callosum. There was no skull fracture. Although microscopical study revealed no sign of other renal disease there were pigment casts in the collecting tubules. This finding together with the fact that there was much damage to muscle-tissue about the fracture-dislocation of the elbow suggests that oliguria was due to "crush syndrome".

TABLE IV.
CAUSES OF DEATH — 30 CASES

Concussion	8 cases
Compression + concussion	11 "
Compression	2 "
Brain-stem hæmorrhage	3 "
Meningitis	1 "
Miscellaneous (not directly related to head injury)	5 "

Bronchopneumonia was present in 8 of the 27 cases in which the lungs were examined. While it is difficult to estimate the degree to which pneumonia had been responsible for producing death it seemed that in all of the cases except one, which has been mentioned, its rôle was clearly secondary. Bronchopneumonia was estimated to be well developed in 4 cases and mild in 4 cases.

DISCUSSION

This small series illustrates the variety of lesions occurring in fatal cases of acute head injury and permits examination of some of the factors concerned in their production. It also allows an evaluation of the importance of certain lesions in causing death in cases of this type.

Skull fracture, while not invariable, occurred in the majority of cases. The base of the skull was involved in nearly every case, either by a fracture confined to the base or by extension of a fracture of the cranial vault. Lecount and Apfelbach,[4] who found both base and vault to be involved in 92% of a series of 500 cases of skull fracture, accept as fundamental the tendency of fractures of the skull to radiate up into the vault and down into the base. The present series shows particularly well how the bony buttresses of the skull base, the thickened ridges of bone forming the borders of the cranial fossæ, caused extension of the fracture lines towards the body of the sphenoid bone where these buttresses meet, with fracture of this bone in over one-half the cases. The risk of extension of infection from fractured paranasal sinuses or middle ears is well known and this occurred as a consequence of sphenoid fracturing in one case in this series, producing fatal meningitis. A further complication of fractures involving sinuses may be intracranial pneumatocœle, as has been pointed out by Eaglesham.[5] Attention is directed to the frequency of sphenoid involvement, as the radiological diagnosis may be difficult and the presence of a cerebrospinal fluid leak into the naso-pharynx may be masked.

A proportion of the surface lacerations and contusions of the brain occurring in cases of acute head injury are explained by the direct traumatizing effect of depressed comminuted bone fragments upon the underlying cortex. In the absence of depressed fracture it has been postulated that localized injury to the brain at the point of violence to the head may be caused by momentary inbending of the skull, with or without fracture. That a large number of cerebral lacerations are not due to either of these causes is well known and the mechanism of such damage has been the subject of many theories. These theories were formulated to explain the occurrence of lesions at situations in the brain directly opposite the point of application of violence to the skull, that is, in the

contrecoup situation. A basic observation, made by Lecount and Apfelbach was that the occurrence of brain lesions in the contrecoup situation depended upon the head being in motion at the time of injury. The present series of cases demonstrates that surface lacerations of the frontal and temporal poles result from violence to the moving head in either the occipital or frontal regions, the lesions being contrecoup in the first and coup in the second instance, and that the occipital region of the brain escapes gross injury. This observation has been emphasized by Courville[6] who also stressed that the anatomical relationships between the brain and the adjacent bony surfaces probably determine the nature and distribution of the cerebral surface lesions. He pointed out that the frontal and temporal poles and subfrontal and subtemporal surfaces, favourite sites of surface lacerations, are in contact with rough irregular bony surfaces, while the occipital areas which usually escape damage are supported by the tentorium, the posterior part of the cerebral falx and the smooth concave surface of the occipital bone.

The recent work of Holbourne[7] concerning the physical mechanism of head injury provides an explanation for the production of cerebral lacerations which is in agreement with these observed facts. He believes that in the majority of cases of damage to the brain the so-called contrecoup lesions are caused by severe shearing strains brought about by rotatory movements of the brain within the skull. Moving pictures of complex movements of the brain following trauma to the head have been made by Shelden, Pudenz and Ristorski[8] in monkeys equipped with lucite skull-caps. Holbourne points out that the greatest shear forces develop where there are projecting bony irregularities, thus accounting for the constant anatomical distribution of brain lacerations in sites where the skull can get "a good grip" on the brain as it rotates.

As has been indicated, surface lacerations are not considered to be of prime importance in the immediate prognosis of cases of head injury and may for the most part be considered in Jefferson's[9] term as "epiphenomena". There is one exception to this, however. As has been stressed by Botterell and by Stewart, massive laceration of the frontal or temporal poles, due to movement of the brain within the skull, contrecoup to the site of application of violence, with tearing of the arachnoid, may result in the pouring of pulped brain mixed with blood and cerebrospinal fluid into the adjacent subdural space. Stewart encountered this lesion in 22 of 798 craniocerebral injuries admitted to the neuro-surgical service of this hospital over a period of three years ending in May, 1944. Stewart points out that after a period of 5 to 10 days such an "exploded" temporal or frontal pole begins to act as a rapidly expanding space-occupying lesion, causing generalized increased intracranial pressure, not due to continued bleeding. He states that diagnosis of this type of lesion depends upon an awareness of its existence and the mechanism by which it is produced. The surgical treatment is removal of damaged brain and the subdural collection of blood and pulped brain tissue, which provides an internal decompression as well.

The intracerebral hæmorrhages encountered in this series occurred both in the cerebral hemispheres and in the brain stem. They were for the most part small, but 3 cases in which large intracerebral hæmorrhages were met with are reported. Some have doubted the occurrence of massive intracerebral hæmorrhage due to violence to the head in the absence of previous disease of the vessels. It is believed that in these 3 cases this eventuality is precluded and that in these cases trauma alone caused the hæmorrhages. There is some question as to whether hæmorrhages into the brain stem and pons have a different etiology from those in the cerebral hemispheres. Van Geheuten[10] drew attention to such hæmorrhages found sometimes in association with a tentorial pressure cone and considered the bleeding due to terminal vasomotor paralysis. Moore and Stern[11] in studying such hæmorrhages sometimes found in cases of fatal brain tumours formed the opinion that they were due to a sudden rise in intracranial pressure. In cases of acute head injury the problem is to discover whether such lesions are due directly to trauma or are secondarily related, being caused by increased intracranial pressure. In 7 of the 10 cases hæmorrhages were present in the sites under consideration associated with autopsy evidence of increased intracranial pressure. However, in only 2 of these 7 cases was the compression rated as severe. The association in 8 of 10 cases of midbrain and pontine lesions with similar lesions in the cerebral hemispheres would seem to indicate a common mechanism

in the majority of cases probably related to complex movements of the brain inside the skull. However, agreement has not been reached as to the mechanics of hæmorrhage in this situation and it may be that a sudden rise in intracranial pressure secondary to head injury can produce midbrain lesions in some cases.

In the present series the lethal importance of concussion, either alone or in combination with other factors, has been stressed. It is not my intention to discuss the mechanism of the production of concussion, or its nature, beyond noting that recent experimental work would appear to indicate that it is an immediate traumatic paralysis of reflex function associated with generalized intracellular neuronal disorder. Definitions of concussion encountered in the literature on the subject are based on the clinical picture in non-fatal cases, and would not lead one to suppose that the condition may result in death. Trotter[12] states that it is "an essentially transient state". Denny-Brown[13] defines it as a "transitory and reversible nervous reaction with immediate onset following physical stress of sufficient violence and brevity, and characterized by progressive recovery thereafter". Despite this, it is generally recognized that death due to the effects of concussion may occur in experimental animals and in humans. Lack of reference to this lethal potentiality in definitions of the condition may be due to the fact that a pathological basis for concussion has not been established, and recognition of it depends upon clinical findings. It is true that some have maintained that the condition is due to the presence of hæmorrhagic lesions, but Denny-Brown and Russell[14] have shown that in experimental concussion the mechanism is independent of cerebral or spinal hæmorrhage or contusion, and have observed fatal concussion in the absence of brain lesions in acute experiments.

Cases of death from head injury in the absence of visible lesions likewise have been reported, and Jefferson has pointed out that in many cases in which death occurs the brain lesions, although present, do not seem sufficient to cause death. Recently Windle, Groat and Fox[15] have described certain delayed microscopical neuronal changes occurring in animals with experimental concussion, but specific histopathological changes have not been demonstrated in humans. Hence, as Denny-Brown and Russell point out, "the only criterion so far accepted is death without lesions". At present, therefore, the diagnosis of concussional death depends on a clinical history of unconsciousness from the time of severe head injury until death, coupled with absent or insignificant findings in the central nervous system at autopsy. Realization of this should lead the pathologist to consider the possibility of concussional death in cases of acute fatal head injury in which visible cerebral lesions are absent or trivial. As has been indicated, uncomplicated cerebral lacerations, even when large, are to be considered in the latter category.

SUMMARY

The autopsy findings in 30 cases of acute craniocerebral injury occurring in soldiers have been presented. The various patterns of bony and cerebral damage encountered have been reviewed and an attempt has been made, to evaluate their importance in causing death.

REFERENCES

1. BOTTERELL, E. H.: Personal communication.
2. STEWART, O. W.: *Proc. Roy. Soc. Med.*, 37: 381, 1944.
3. BOTTERELL, E. H. AND WILSON, K. E.: *Canad. M. A. J.*, 51: 498, 1944.
4. LECOUNT, E. R. AND APPELBACH, C. W.: *J. Am. M. Ass.*, 74: 501, 1920.
5. EAGLESHAM, D. C.: *Brit. J. Radiol.*, 18: 335, 1945.
6. COURVILLE, C. B.: *Arch. Surg.*, 45: 19, 1942.
7. HOLBOURN, A. H. S.: *The Lancet*, 145: 438, 1943.
8. SHELDEN, C. H., PUDENZ, R. H. AND RESTORSKI, J. S.: *J. Neurosurg.*, 1: 67, 1944.
9. JEFFERSON, G.: *Glasgow M. J.*, 20: 77, 1942.
10. VAN GEHEUTEN, P.: *Encéphale*, 32: 133, 1937.
11. MOORE, M. AND STERN, K.: *Brain*, 61: 70, 1938.
12. TROTTER, W.: *The Lancet*, 1: 935, 1924.
13. DENNY-BROWN, D.: *Physiol. Rev.*, 25: 296, 1945.
14. DENNY-BROWN, D. AND RUSSELL, W. R.: *Brain*, 64: 93, 1941.
15. WINDLE, W. F., GROAT, R. A. AND FOX, C. A.: *Surg., Gyn. & Obst.*, 79: 561, 1944.

AN EVALUATION OF VARIOUS FORMS OF THERAPY IN EARLY SYPHILIS*

Frederick Kalz, M.D. and Barbara Dean, M.D.

Montreal, Que.

THE problem of syphilis therapy has been to evolve a form of treatment which would achieve biological cure in the greatest number of patients, and in the shortest period of time, without causing toxic reactions. In this attempt, effective but dangerous treatment schemes have been tried but had to be abandoned. Penicillin therapy has evoked great hopes and this form of treatment has gradually replaced the arsenicals in many clinics and was used in the majority of cases of early syphilis

* From the Section of Dermatology, Subdepartment of Medicine, Royal Victoria Hospital, Dr. J. C. Meakins, Physician-in-Chief.

in the Royal Victoria Hospital, Montreal, during the last two years.

From January 1, 1937 until June 30, 1946, 401 cases of early syphilis have been treated with some form of arsenical therapy. We will report in the first part of this paper on the serological results in 241 cases and the treatment reactions of 243 patients, omitting 62 patients who had arsenical therapy prior to admission to our clinic, and 98 patients who were either observed for less than 18 months or transferred to another hospital before the S.T.S. reversed. These 241 patients were followed until the serological reactions turned negative, or at least 18 months from start of treatment.

TABLE I.
TYPES OF TOXIC REACTIONS IN 93 PATIENTS

	All drugs	*5-day*	*Mapharsen*	*Clorarsen*	*Neoarsphenamine*	*Old arsphenamine*
Number of patients treated by each drug	243*	49	167	32	127	23
Number of patients reacting to each drug	93 (38.59%)	25 (51.02%)	50 (29.94%)	9 (28.13%)	23 (18.11%)	5 (21.74%)
Minor reactions	67 (27.8%)	21 (42.86%)	36 (21.56%)	5 (15.63%)	14 (11.02%)	1 (4.35%)
Systemic reactions	12 (4.98%)		11 (6.59%)	3 (9.38%)	1 (0.79%)	
Toxic erythema	9 (3.73%)	5 (10.2%)	2 (1.19%)	1 (3.13%)	1 (0.79%)	1 (4.35%)
Post-arsphenamine dermatitis	1 (0.42%)				1 (0.79%)	
Other skin reactions**	6 (2.49%)		3 (1.8%)		2 (1.57%)	1 (4.35%)
Neuritis	1 (0.42%)				1 (0.79%)	
Hepatitis	2 (0.83%)				2 (1.57%)	
Blood dyscrasia	1 (0.42%)				1 (0.79%)	
Encephalopathy	3 (1.24%)	2 (4.08%)			1 (0.79%)	
Nitritoid reaction	6 (2.49%)				3 (2.36%)	3 (13.04%)

*Several patients showed toxic reactions to more than one drug.
**Other skin reactions include pityriasis rosea and lichen planus-like eruptions.

Seven patients were sero-negative primaries and were not included in the tables dealing with serological reversal.

These figures correspond closely to the results obtained in larger series. Mapharsen produced a high number of minor reactions, most of which were of harmless nature but still often necessitating a change of drug, or were sufficiently unpleasant to cause the patients to lapse in their attendance. The dangerous reactions are conspicuous by their absence (if the drug is not given more than three times a week), which has been confirmed by clinical experience[1] and by animal experiments.[2] Neoarsphenamine has a lower total incidence of reactions but many of the cases of intolerance constitute severe and dangerous complications. The difficulties in differentiating arsenical hepatitis from infectious hepatitis are realized and the diagnosis in the two cases listed was made on the basis of concomitant post-arsphenamine dermatitis in one case and a toxic erythema in the second case.

From the incidence of serious reactions reported in the literature,[1] as well as from our material, it appears that neoarsphenamine should be avoided altogether in the treatment of early syphilis, and it is now being used in our clinic only in those patients who cannot attend twice weekly for treatment with one of the arsenoxides. The same may be said for old arsphenamine which we formerly employed in patients in whom very active treatment was indicated, such as serologic or clinical relapse, or early neurosyphilis. We have discontinued using this drug, replacing it by penicillin combined with arsenoxides, or fever treatment, or both.

Clorarsen shows a relatively high number of minor reactions in this table which may be misleading since we used that drug chiefly as an alternative in sensitive patients who exhibited intolerance to mapharsen or neoarsphenamine. The incidence of reactions appears low and many patients who did not tolerate any other arsenical could continue therapy using clorarsen.[3]

Massive arsenotherapy or 5 day treatment may be considered obsolete, because penicillin, perhaps in combination with subcurative dosage of arsenoxide and bismuth, answers the demand for a method rendering patients rapidly non-infectious and has no dangerous side effects. The percentage of cure is comparable to that achieved with massive arsenotherapy which, therefore, in our opinion should not be used. We have tried massive arsenotherapy for in-

vestigative purposes only, and our endeavour to find a laboratory method which would indicate threatening encephalography in time was not successful,[4] and two cases of encephalopathy terminated fatally.[5] Two cases of encephalopathy caused by neoarsphenamine given outside of this hospital were observed lately and we believe that the use of BAL[6] was responsible for the quick recovery noted. The same favourable result was observed in two patients with post-arsphenamine dermatitis.

We feel justified in concluding from this table of toxic reactions that the use of toxic drugs or dangerous treatment schemes is no longer justified. Arsenoxide, given not more than three times weekly, does not produce dangerous reactions, and proved, in our hands, a satisfactory type of therapy in most cases.

The following tables show the serologic response of 241 patients, comparing the following treatment schemes.

1. *Arsenoxide* (mapharsen or clorarsen), twice weekly, until a total of fifty injections, usually in a dosage of 0.06 gm., had been given.

2. *Arsenoxide,* once weekly, until 40 to 60 injections in single dosage of 0.06 gm. had been given.

3. *Neoarsphenamine,* single dosage usually 0.6 gm. until 40 to 60 injections had been given.

4. *Arsphenamine* (606), single dosage varying from 0.4 to 0.5 gm. until 40 injections had been given.

5. *Mixed arsenicals,* that is in cases in which change of drug was indicated because of intolerance, until 40 to 60 arsenicals had been given.

All these arsenicals were given in conjunction with alternating and overlapping courses of bismuth subsalicylate, once weekly, until 30 to 50 injections had been given. Attendance is considered regular if patient attended more than 75% of scheduled visits.

6. *Massive arsenotherapy,* either 5 day drip or multiple injections for about 10 days, in total dosage of 1,200 to 1,300 mgm. of arsenoxide.

The blood Wassermann reaction using a quantitative technique and the standard Kahn were done in all cases and repeated in most patients at least monthly until reversal occurred.

TABLE II.

AVERAGE TIME REQUIRED TO ACHIEVE COMPLETE SEROLOGICAL NEGATIVITY IN ALL CASES OF EARLY SYPHILIS USING VARIOUS SCHEMES OF ARSENOTHERAPY

	All cases		*Regular attendance*		*Irregular attendance*	
Treatment scheme	*Number of cases*	*Time in weeks*	*Number of cases*	*Time in weeks*	*Number of cases*	*Time in weeks*
All treatment schemes	190	29	103	24	45	44
Arsenoxide twice a week	59	22	46	19	13	34
Arsenoxide once a week	22	35	14	27	8	50
Neoarsphenamine	38	32	23	24	15	44
Mixed arsenicals	22	43	13	34	9	55
Old arsphenamine	7	36	7	36		
Massive arsenotherapy	42	23				

It is interesting to note that the average time for achieving seronegativity was shortest with arsenoxide twice weekly, massive arsenotherapy taking an intermediate position, while other schemes required considerably longer.

TABLE III.

AVERAGE TIME REQUIRED TO ACHIEVE COMPLETE SEROLOGICAL NEGATIVITY IN THE VARIOUS STAGES OF EARLY SYPHILIS

	All cases		*Regular attendance*		*Irregular attendance*		*Intensive arsenotherapy*	
Diagnosis	*Number of cases*	*Time in weeks*	*Number of cases*	*Time in weeks*	*Number of cases*	*Time in weeks*	*Number of cases*	*Time in weeks*
All early syphilis	190	29	103	24	45	44	42	23
Primary syphilis	38	19	28	20	3	28	7	9
Secondary syphilis	101	27	50	23	20	41	31	26
Relapsing secondary syphilis	10	38	8	35	1	45	1	56
Early asymptomatic syphilis	41	39	17	31	21	50	3	10

This table shows the established fact that the duration of the infection is one of the determining factors of serological response.

For the purpose of preparing this table we have arbitrarily considered neoarsphenamine 0.6 gm., arsphenamine 0.4 gm., and clorarsen 0.067 gm., equivalent to mapharsen 0.06 gm. While the equation is not exact, it was chosen because these doses are commonly used in routine therapy.

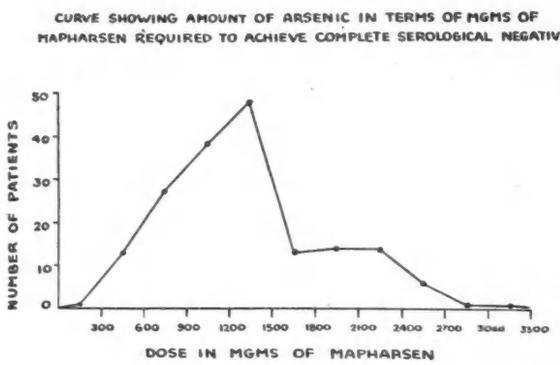
It is of interest to note that there is little variance in the total amount of arsenicals required to bring about serological reversal irrespective of the drug used.

The curve shows graphically that 1,200 to 1,300 mgm. of arsenoxide will bring about serological reversal in most cases (181 cases).

TABLE IV.

AVERAGE DOSE, IN TERMS OF MILLIGRAMS OF MAPHARSEN, REQUIRED TO ACHIEVE COMPLETE SEROLOGICAL NEGATIVITY IN ALL CASES OF EARLY SYPHILIS, USING VARIOUS SCHEMES OF ARSENOTHERAPY

	All cases		*Regular attendance*		*Irregular attendance*	
Treatment scheme	*Number of cases*	*Mgm. of mapharsen*	*Number of cases*	*Mgm. of mapharsen*	*Number of cases*	*Mgm. of mapharsen*
All treatment schemes....	181	1,337	100	1,314	42	1,420
Arsenoxide twice a week...	58	1,476	45	1,437	13	1,609
Arsenoxide once a week ...	20	1,104	12	1,025	8	1,223
Neoarsphenamine.....	35	1,096	23	1,093	12	1,100
Mixed arsenicals.....	22	1,624	13	1,537	9	1,750
Old arsphenamine.....	7	1,331	7	1,331		
Massive arsenotherapy....	39	1,308				



same trend as in other tables is visible, patients treated with arsenoxide twice a week having the lowest incidence of serological relapse, and patients who receive massive arsenotherapy and those who attended irregularly, the highest, arsenicals once weekly taking an intermediate position.

It appears that mapharsen given regularly, twice weekly, was the most effective drug in bringing about serological reversal.

Serological reversal is evidence of a favourable prognosis in most cases, but it is by no means a criterion of biological cure because a certain percentage of clinical or serological relapses will occur. A long period of observation is required to determine the eventual outcome. Follow-up procedures should include regular serological check-up, clinical observation, and

TABLE V.

AVERAGE DOSE, IN TERMS OF MILLIGRAMS OF MAPHARSEN, REQUIRED TO ACHIEVE COMPLETE SEROLOGICAL NEGATIVITY IN THE VARIOUS STAGES OF EARLY SPYHILIS

	All cases		*Regular attendance*		*Irregular attendance*		*Intensive arsenotherapy*	
Diagnosis	*Number of cases*	*Mgm. of mapharsen*	*Number of cases*	*Mgm. of mapharsen*	*Number of cases*	*Mgm. of mapharsen*	*Number of cases*	*Mgm. of mapharsen*
All early syphilis.....	181	1,337	100	1,314	42	1,420	39	1,308
Primary syphilis.....	37	1,210	27	1,192	3	1,353	7	1,217
Secondary syphilis.....	95	1,315	48	1,342	19	1,297	28	1,282
Relapsing secondary syphilis.	10	1,458	8	1,357	1	780	1	2,940
Early asymptomatic syphilis.	39	1,481	17	1,409	19	1,587	3	1,220

Table V brings out the same points as Table II, namely the influence of the duration of infection on the time and the amount of arsenicals, required to achieve serological reversal.

TABLE VI.

ANALYSIS OF TREATMENT FAILURES

	All treatment schemes	*Intensive arsenotherapy*	*Mapharsen twice a week regular attendance*	*Arsenical once a week regular attendance*	*Irregular attendance*
Number of patients treated..	243	57	49	71	67
Number of treatment failures	37 (15.35%)	13 (24.07%)	1 (2.04%)	9 (12.68%)	14 (20.9%)
Fixed serological tests.....	16 (6.64%)	2 (3.7%)		6 (8.45%)	8 (11.94%)
Serological relapse.....	12 (4.98%)	5 (9.26%)	1 (2.04%)	2 (2.82%)	4 (5.97%)
Clinical relapse.....	5 (2.07%)	3 (5.56%)			2 (2.99%)
Clinical progression.....	2 (0.83%)	1 (1.85%)		1 (1.41%)	
Death during treatment.....	2 (0.83%)	2 (3.7%)			

Table VI shows all failures observed, during and after conclusion of therapy, in patients under varying lengths of observation. The

TABLE VII.

	No. of patients	*Fixed serologic tests after 18 mos.*
Total	241	22
Massive arsenotherapy	54	2
Arsenoxide twice a week	49	0
Arsenical once weekly:		
Regular	71	6
Irregular	67	14

repeat of cerebrospinal fluid examination when indicated.

In our series of 241 patients, only 131 meet these requirements.

TABLE VIII.
FOLLOW-UP OF PATIENTS WITH EARLY SYPHILIS

1—2 years	2—3 years	3—7 years	
42	46	43	= total 131 patients

The final results as observed in these patients are listed as follows:

Fourteen of the 23 patients included in the group "failures" were re-treated by intensified arsenical therapy, penicillin, or artificial fever, or combinations of these procedures were used.

TABLE X.
EVENTUAL OUTCOME OF 23 CASES DESCRIBED AS "FAILURES"

Satisfactory	15
Doubtful	7
Unsatisfactory	1

The above demonstrates that resistance to therapy in early syphilis is relative and can, in most instances, be overcome by changing or intensifying the treatment plan.

The one case listed as unsatisfactory presents the following points of interest:

M.L., 32 years. This prostitute was first seen with mucocutaneous secondary syphilis. Her blood Wassermann was positive in a titre of 1:256. Treatment was started with 0.02 gm. of mapharsen only because of extensive mucous patches. A rather severe febrile Herxheimer reaction ensued. She was then given mapharsen 0.03 gm. and 0.06 gm. which resulted in a toxic erythema on the flexor surfaces; treatment was interrupted for one week, then resumed, after disappearance of the erythema, in the same dosage. The erythema again appeared and, after the next injection, a widespread maculo-papular erythema occurred and the patient was hospitalized. Treatment was resumed after three weeks, using clorarsen 0.045, and the signs and symptoms of secondary syphilis subsided quickly in the usual manner. Treatment was continued using clorarsen 0.045 gm. to 0.067 gm., mostly only once a week, because after every injection a mild erythema was noted and general malaise was observed. The erythema, although it appeared after every injection, remained localized on the flexor surfaces and was eventually ignored by us as well as by the patient.

Repeated cerebrospinal fluid examinations were normal. The blood Wassermann reaction decreased somewhat in titre but when therapy was concluded it was still positive in a titre of 1:48. Because of this she was given artificial fever therapy, 12 weekly treatments with a total of 50 hours over 105° F. During this period she received 12 arsenicals at the height of fever and 12 injections of bismuth the evening before. The blood Wassermann titre remained unchanged and after another year she was re-admitted to hospital. She received 5,000,000 units of penicillin in conjunction with 320 mgm. of arsenoxide and 0.8 gm. of bismuth. To date, 12 months after conclusion of penicillin therapy, blood Wassermann reaction is still positive in a titre of 1:16. The gradual decrease of the titre makes it likely that complete serological reversal will eventually take place, and since the cerebrospinal fluid remained normal throughout, and as there are no signs of clinical progression or relapse, the patient will probably be listed under the group of satisfactory treatment results at some time.

TABLE IX.

	All patients	*Arsenoxide twice weekly*	*Other treatment schemes*		*Massive arsenotherapy*
			Regular	*Irregular*	
Total	131	28	40	22	41
Satisfactory	108 (82%)	28 (100%)	34 (85%)	15 (68%)	31 (75%)
Doubtful	4 (3.5%)	0	2 (5%)	1 (4.5%)	1 (2.4%)
Failures	19 (14.5%)	0	4 (10%)	6 (27%)	9 (21%)

By satisfactory outcome is meant that patients remained clinically and serologically negative and cerebrospinal fluid showed normal results.

By doubtful outcome is meant that patients were clinically normal, with normal cerebrospinal fluid, but serological tests (blood Wassermann or Kahn test) remain doubtful, or positive in a titre of less than two units.

Failures mean those cases showing serological or clinical relapse, abnormal cerebrospinal fluid findings, or those in which serological reversal did not occur.

Our results correspond to the results obtained by many authors in large series. The favourable outcome of regular therapy with arsenoxide is striking, even considering the small number of patients, and equally conspicuous are the poor results obtained with irregular therapy. The group designated "other treatment schemes" comprises those patients treated with mapharsen or neoarsphenamine once a week, or those in whom the treatment scheme was changed.

It is most likely that the cases included in the doubtful group will eventually show a spontaneous serological reversal, and a favourable clinical outcome is to be expected.[7]

One may assume in this case that the small dose of mapharsen at the beginning of therapy caused a relative "fastness" of the spirochætes to arsenicals. The repeated erythema was unique in our experience.

Forty-eight patients have been treated with penicillin and were observed from 6 to 22 months. The dosage varied from 1,200,000 to 10,000,000 units given over a period of from 8 to 12 days and in the majority was combined with about 300 mgm. of arsenoxide and 0.6 mgm. of bismuth subsalicylate. In 26 patients serological reversal was observed and the average time to achieve complete sero-negativity was 29 weeks. This was exactly the average time we observed as over-all figure for all schemes of arsenotherapy but slower than that seen with arsenoxide twice weekly or with massive arsenotherapy (22 weeks).

There was no definite relation to the initial titre of the blood Wassermann reaction although it appeared that very high titres required somewhat more time for complete reversal. There was no relation to the amount of penicillin given and no difference was seen between those cases which received concurrent arsenotherapy and those who did not.

The longest time required for complete sero-negativity was 19 months, the shortest 4 months (omitting the cases of primary syphilis); 23 patients were observed over a period of from 12 to 22 months.

TABLE XI.

	Total	*Presumed cured*	*Failure*
Cases	23	19	4
Primary	6	6	0
Secondary	12	9	3
Early latent syphilis	5	4	1

We considered as failures such cases in which the S.T.S. failed to reverse within 12 months or in which a significant rise in titre occurred after an initial fall.

Two of these patients received 1,200,000 units of penicillin combined with arsenoxide, both listed as presumably cured. Eight patients received 2,500,000 units of penicillin without concurrent arsenotherapy, 7 of which appeared to be cured while 1 of them was listed a failure. The remaining 3 failures received 5,000,000 units of penicillin combined with arsenicals.

The material is too small and the period of observation too short to draw valid conclusions. It appears from the flood of recent publications that one may expect from 10 to 20% failures, which seems to be borne out by our small series. These figures are identical with the results observed with massive arsenotherapy, and lately we have followed penicillin treatment by six months' treatment with arsenoxide, a scheme which, so far, has appeared suitable in reducing the number of failures to a minimum.

SUMMARY

1. Two hundred and forty-three patients with early syphilis under various treatment schemes were studied with regard to treatment reactions. We found that mapharsen caused many minor reactions, but severe toxic reactions were almost non-existent, if the drug was not given more than 3 times weekly. Neoarsphenamine caused fewer reactions but these were more severe and its use in routine therapy is, therefore, subject to serious objections. Massive arsenotherapy should not be used considering the unavoidable incidence of encephalopathy and in view of the effectiveness of treatment schemes using penicillin alone, or in conjunction with subcurative and non dangerous doses of arsenicals and bismuth.

2. Two hundred and forty-one patients with early syphilis were studied with regard to serological response to various treatment schemes. Arsenoxide given twice weekly with alternating and overlapping courses of bismuth proved most effective with regard to the number of serological reversals, the period of time required to achieve reversal, and the number of serological relapses observed. Tables II, IV, VI, VII, IX and X present these points.

3. One hundred and thirty-three patients were followed for a period of 1 to 7 years and after conclusion of treatment they were studied with regard to final results of therapy. Among patients treated with massive arsenotherapy, the highest number of unsatisfactory results were observed, no failures were observed in patients treated with arsenoxide twice weekly in this group. Other treatment schemes took an intermediate position.

4. Twenty-three patients who did not respond satisfactorily to routine therapy were observed further and 14 of them were re-treated. Eventual satisfactory outcome occurred in 15 cases, 7 are still designated as doubtful and one case displaying considerable resistance to therapy is reported briefly.

We believe that resistance to therapy is relative only, and can be overcome in most instances by change of drug or intensification of therapy. We observed that of all treatment schemes used prior to the advent of penicillin, arsenoxide given twice a week with alternating and overlapping courses of bismuth proved to be the only safe yet effective form of therapy.

Penicillin therapy proved fairly satisfactory but thorough follow-up is essential since about 10 to 20% of treatment failures will occur. Increase of the total dosage above 2,000,000 units does not seem to alter the percentage of failures. The value of concurrent treatment with arsenicals and heavy metals was not apparent in our small series.

REFERENCES

1. MOORE, J. E.: The Modern Treatment of Syphilis, 2nd ed., Charles C. Thomas, Springfield, Ill., U.S.A.
2. EAGLE, H. AND HOGAN, R. B.: *Science*, **95**: 360, 1942.
3. KALZ, F., EREAUX, L. P., PRICHARD, H. AND DEAN, B.: *Canad. M. A. J.*, **50**: 237, 1944.
4. HOFFMAN, M. M. AND KALZ, F.: *Am. J. Syph., Gonor. & V.D.*, **29**: 596, 1945.
5. HINDS, E. AND KALZ, F.: *Am. J. Syph., Gonor. & V.D.*, **30**: 78, 1946.
6. EAGLE, H. AND MAGNUSSEN, H.: *Am. J. Syph., Gonor. & V.D.*, **30**: 420, 1946.
7. THOMAS, E. W.: *Am. J. Syph., Gonor. & V.D.*, **30**: 317, 1946.

IDIOPATHIC HYPOPLASTIC ANÆMIA WITH BONE MARROW HYPERPLASIA*

Edward S. Mills, M.Sc., M.D., C.M., F.R.C.P.[C.]

Montreal, Que.

A RAPIDLY progressive irreversible depletion of marrow-produced cells without evidence of regeneration is an easily identified clinical picture, but some of the variables of primary aplastic or hypoplastic anæmia are more difficult diagnostic problems. They are differentiated with some difficulty from such diseases as aleukæmic leukæmia, carcinomatosis, multiple myeloma, achrestic anæmia and hæmorrhagic purpura. The following three cases are interesting variants from what is often regarded as the classical description of the disease and they are the only instances of the disease found in the records of the Montreal General Hospital between the years 1937 and 1945.

CASE 1

B.D., aged 25, was first taken ill in September, 1931, at the age of 12 years, and was admitted to hospital on November 14, 1931. His complaints were vomiting, pallor of the skin and headaches. The only abnormalities on physical examination were striking pallor of the skin and a palpable spleen.

Transfusions at once brought relief from his symptoms, but the anæmia returned and splenectomy was performed on January 12, 1932. The pathologist found little wrong with the spleen except fibrosis so it is not surprising that improvement in the anæmia did not follow.

In January, 1933, he developed pneumococcic pneumonia with purulent pericarditis which was drained surgically and following recovery from this infection he enjoyed a remission in his anæmia lasting several months. However, in the following November he was back in the hospital with a red count under one million and a hæmoglobin of 14%. From this time onwards he received at least one transfusion every three weeks which always relieved his headache but seldom brought his erythrocyte level above two million.

During these important years from the age of 12 to the age of 23 his erythrocyte count was over 2 million and the hæmoglobin above 50% on only one occasion (see Table I). And yet he grew from a child to an adult, healthy and normal in all respects save the profound anæmia, and a curious diffuse slate-like pigmentation of the skin.

From 1931 to 1943 he received 196 transfusions of 500 c.c. each, or 98 litres of blood, which never failed to give relief from his headaches and weakness.

During the month of May, 1943, he reported to the outpatient department with the story that he felt well and had taken a position, though the hæmoglobin was only 52%. The following month his blood was approaching normal and as the table shows it remained normal until November, a period of six months.

Unfortunately in March, 1944, he contracted a fatal pneumococcic infection (Type xxiii) with purulent meningitis and endocarditis. Autopsy revealed an ulcerative endocarditis which was the cause of death and a generalized hæmosiderosis. The bone marrow was everywhere markedly hyperplastic particularly the erythroblastic elements. No other abnormalities were found.

Table I records many of the blood values in this case.

Bone marrow biopsies.—The first bone marrow biopsy was undertaken in June, 1934, approximately 33 months after the onset of the illness and over two years after splenectomy. Marrow was obtained from the upper and middle thirds of the tibia. The sections from both of these areas showed marrow which was partly cellular and partly fatty but by no means aplastic. It was regarded by the pathologist as normal marrow. Microphotographs 1 and 2 were taken at this time. In November, 1942, after eight years of severe anæmia rib marrow was obtained and the sections of this showed hyperplasia of myeloid and erythropoietic elements. Microphotograph 3 indicates the absence of fat and the abundance of cellular marrow. Microphotograph 4 shows the appearance of the sternal marrow at autopsy. The marked cellular hyperplasia is evident.

CASE 2

R.H., an English-Canadian child of 6½ years, was admitted to the Montreal General Hospital on June 10, 1936, because of pallor and weakness. The past history was that of any rugged healthy child. About April 1, 1936, the child developed a head and chest cold which lasted a month. This was followed by a skin rash suggesting chickenpox. Thereafter his course was more rapidly downhill. This period was characterized by severe headaches, progressive weakness and pallor, pains in the legs and abdomen, and anorexia.

At the time of admission he appeared pale, weak, and apathetic, though not undernourished. The positive findings were: (1) marked waxy pallor; (2) palpable liver and spleen; (3) cardiac enlargement with to and fro murmurs at apex; (4) chronically infected tonsils with a regional adenopathy.

During the first 2½ months in the hospital he was repeatedly transfused. He ran an irregular fever, appeared extremely ill and developed indolent infections at the sites of incisions for transfusions and rib marrow biopsy.

* From the Departments of Medicine, McGill University and the Montreal General Hospital.

About September 1, he began to improve. The size of the heart became normal and the murmurs disappeared. The hæmogram improved, the infections cleared up and his appetite returned. From then on his convalescence was uneventful. Teeth and tonsils were removed before discharge.

Laboratory data.—Electrocardiograph normal; Wassermann and Mantoux (1/1,000) negative; adrenalin test—no response; urinalysis—normal; basal metabolic rate +10 to +13; hæmograms—see Table II.

The clinical course after discharge was uneventful until the spring of 1937 when his former symptoms recurred and he was readmitted in August. His appearance was similar to that at the time of his former admission. He died after a severe transfusion reaction.

Autopsy revealed no findings of note other than those in the bone marrow. The liver weighed 1,510 gm., the spleen 270 gm. Neither of these organs showed any striking abnormality.

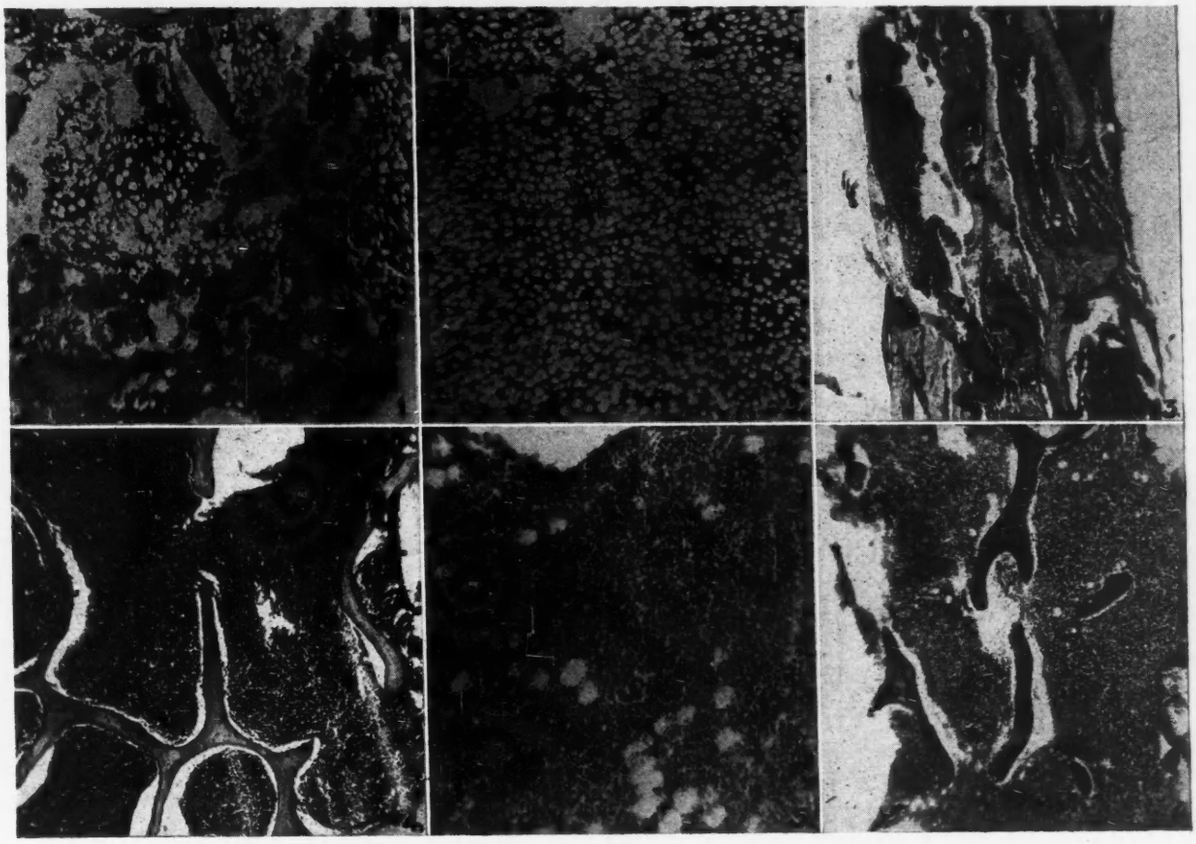
Bone marrow.—The bone marrow of July 20, 1936, was taken from a rib. It was compact and cellular, not fatty. Pathologist's diagnosis—erythroblastic hyperplasia. At autopsy sections were taken from femoral and vertebral marrow. These showed a compact cellular marrow with focal erythroblastic hyperplasia. The myeloid cells and megakaryocytes appeared reduced in

TABLE I. [B.D.]

Date											
Month	*Year*	*R.B.C.*	*W.B.C*	*Hgb.*	*Plat.*	*RR's*	*Pn.*	*L*	*Eos.*	*Bas.*	*Remarks*
Nov.	'31	2.31	5.4	43	318		58	28	2	11	
Jan.	'32			*Jan. 12/32—Splenectomy.*							Fragility 0.425—0.325% Nacl.
Apr.	'32	1.99	3.3	45	1992	0.5	64	36			
Jan.	'33										Pneumonia and pericarditis purulent
Nov.	'33	0.75	7.5	14	546		34	47		Monos. 14	
Mar.	'34	1.33	7.3	30	940	>1%	54	30	2	4	B.M.R. -8. Van den Bergh 0.2
				Biopsy shin—normal bone marrow.							
Sept.	'34	1.94	7.1	34	655		49	37	2	Monos. 6	
Jan.	'35	1.41		22	950						
Apr.	'35	1.16		24							
Mar.	'36	1.73	8.3	23		>1%					R.C.D. 7.9 microns.
Feb.	'37	1.40	30.4	30	825						R.C.D. 7.7. Lobar pneumonia
Aug.	'38	1.03	6.1	23	433		72	26	1	1	R.C.D. 7.3
Feb.	'41	2.73	5.1	53	465	1.1%	56	42	2		R.C.D. 7.6. Otitis media. Pneumonia.
Oct.	'42	2.03	9.9	34	355		56	34	5		R.C.D. 7.6. Pneumonia.
				Bone marrow rib—Hyperplastic marrow.							
May	'43			52							R.C.D. 8.4
June	'43	3.94	10.0	88			58	29	2	2	
July	'43			94							
Aug.	'43			90							
Sept.	'43	4.95	7.6	98							R.C.D. 7.7
Nov.	'43			94							
Mar.	'44	2.03	19.2	47	194		72	24	3	2	R.C.D. 8.0. Meningitis type xxiii. Endocarditis.

TABLE II. [R.H.]

Date				Hgb.								
Mon.	*Year*	*R.B.C.*	*W.B.C*	*%*	*Gms.*	*Plat.*	*RR's*	*Pn.*	*L.*	*Eos.*	*Monos.*	*Remarks*
June	10/36	0.96	3,650	16	2.35	118	>1%	26	73			Trans. (1) R.C.D. 7.6 microns
June	16/36		4,600									Trans. (2)
June	24/36		3,650			69	>1%					Trans. (3)
July	2/36		4,750			71						Trans. (4) R.B.C.'s normal
							>1%					Trans. (5)
July	14/36	2.39	2,750	45%	7.35	80						
July	20/36			*Biopsy of rib—compact cellular marrow.*								
July	24/36	2.40	2,500	34%	5.40	99	>1%					Fragility 0.425—0.325%
Aug.	18/36	1.48	3,100	29%	5.90	63						
Aug.	29/36	2.16	2,900	43%	7.15	109						R.C.D. 7.7 microns.
Sept.	8/36	3.17		58%	9.45							
Sept.	17/36	3.09	4,950	60%		217		46	49		2	R.C.D. 7.9 microns
Oct.	8/36	4.20	7,950	76%	12.45							
Oct.	30/36	3.92		75%								
Nov.	10/36			*Tonsillectomy.*								
Dec.	16/36	5.88	9,000	91%		224	>1%	35	54	3	8	
April	14/37	4.60		83%								
Aug.	27/37	1.55	2,800	29%	5.00	165		62	30		4	
												Trans. (6) and (7)
Sept.	9/37	2.65	4,200	54%								
Sept.	13/37	2.20		50%			0.6%					
Sept.	20/37	1.30	4,750	26%		24		62	35		3	
Sept.	22/37	2.24	3,900	50%	6.75			20	80			
Sept.	28/37	1.00		22%	3.00		3.0%					R.C.D. 7.7 microns.



Illustrating the hyperplasia of the marrow in Cases 1 and 2. **Fig. 1.** Case 1.—Upper third tibia, June, 1934. **Fig. 2.** Case 1.—Mid tibia, June, 1934. **Fig. 3.** Case 1.—Rib marrow, November, 1942. **Fig. 4.** Case 1.—Sternal marrow (autopsy), June, 1944. **Fig. 5.** Case 2.—Marrow femur (autopsy), October, 1937. **Fig. 6.** Case 2.—Vertebral marrow (autopsy), October, 1937.

numbers. Foci of small round cells were also noted (see Figs. 5 and 6).

CASE 3

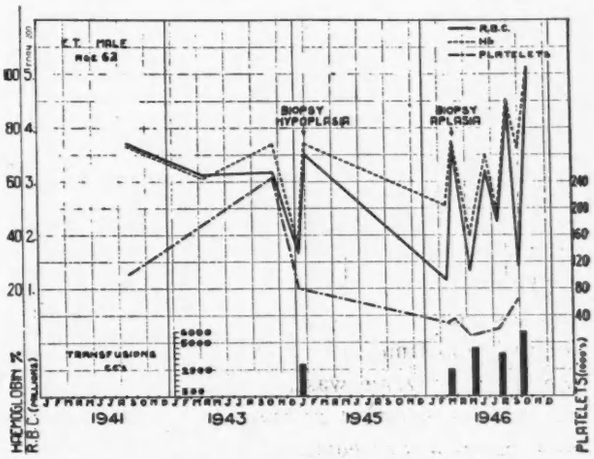
E.T., aged 62, was seen first in Sepember, 1941, because of moderately severe anæmia occurring in the course of a fairly generalized erythema multiforme. The anæmia was of the normocytic type and the leucocyte formula was normal.

He was again seen in April, 1943, because of a non-pneumococcic pneumonia, at which time the hæmogram had not changed. In October of 1943, he was again admitted because of erythema multiforme, erythema nodosum and epididymitis. At this time gastric analysis showed normal values. The basal metabolic rate was normal. In 1944, he was admitted to the hospital because of palmar abscess and lymphangitis following an infected finger.

In January, 1945, the first decided drop in his erythrocyte count, hæmoglobin and platelets were noted but the leucocyte formula was normal. Biopsy of the rib marrow at this time showed hyperplastic myeloid activity but normoblasts, megaloblasts and megakaryocytes were scanty. He received 3 litres of blood which doubled the erythrocyte count.

In March, 1946, all the blood elements were markedly reduced and he was clinically weak, dyspnœic, mildly œdematous with a purpuric rash over the legs. From this time until September he received 17 litres of blood. The details of the hæmograms are recorded in Table III. At this time the bone marrow was aplastic. As the chart shows restoration of the erythrocyte count and the hæmoglobin was readily effected by means of transfusions but the platelet level remained low and this resulted in multiple hæmorrhagic lesions. Death in November, 1946, was due to intracranial hæmorrhages.

The accompanying graph illustrates the fluctuations in the erythrocyte, hæmoglobin and platelet levels. It shows that the thrombocytopenia is not materially affected by transfusions of whole blood in amounts sufficient to raise the erythrocyte level almost to normal limits. It also shows the increasing momentum of the disease as it approached its terminal phase.



COMMENT ON CASES

These three patients illustrate a number of the vagaries of primary aplastic or hypoplastic anæmia. The first patient lived for 13 years after the onset of his illness, during which

TABLE III. [E.T.]

Date											
Month	*Year*	*R.B.C.*	*W.B.C*	*Hgb.*	*Plat.*	*RR's*	*Pn.*	*L.*	*Eos.*	*Monos.*	*Remarks*
Sept.	'41	3.62	7,450	72%	109	3.2%	77	19		4	Cell volume 33%. R.C.D. 7.9 microns. B.M.R. +18.
				Eryt	hema	multif	orme.				
Apr.	'43	3.06	7,250	62%	100		62	32	4		Virus pneumonia—sulfadiazine.
Oct.	'43	3.11	7,450	74%	245	1.2%	59	37	2		C. vol. 36%. Erythema multiforme. Erythema nodosum. Epididymitis —sulfathiazole. Reticulogen. Gastric analysis fractional max. free HCL 43, total acidity 54. B.M.R. +15.
Jan.	'45	1.72	6,150	36%	80	2%	71	24	1		R.C.D. 8.1 *Bone marrow biopsy:—Path.*—Many blast cells, large numbers myelocytes and polys. Only a few nucleated reds and megakaryocytes. *Diag.*—Hyperplastic myeloid bone marrow.
				Er	ythem	a mult	iforme				
				Transf	usions	3,000 c	.c.				
Jan.	'45	3.50	4,600	74%							
March	'46	1.19	3,850	56%	27	>1%					R.C.D. 8.4 microns. Plasma proteins 7.5%. *Sternal puncture*—Red cell aplasia. Transfusions, 2,500 c.c.
March	'46	3.66		74%	30						R.C.D. 7.7 microns. Cell volume 35%
May	'46	1.34	3,450	40%	12	2%	56	40	2		R.C.D. 8.2 microns. Cell volume 15%. Transfusions 4,500 c.c.
May	'46	3.24	5,500	70%							
July	'46	2.25	2,650	48%	20	>1%	30	52		3	R.C.D. 8.1 microns. Transfusions 4,000 c.c.
July	'46	4.45	6,000	90%							R.C.D. 7.7 microns.
Sept.	'46	1.46	3,200	34%	64	>1%	54	33		4	R.C.D. 8.1 microns. Transfusions 6,000 c.c.
Sept.	'46	5.05		101%							R.C.D. 7.7 microns.
Oct.	15/46	4.21	4,300	86%	50	>1%	62	33	1	1	R.C.D. 7.7 microns.
Nov.	13/46	2.07	4,550	41%	70	>1%	36	50	3	1	R.C.D. 7.9 microns.

period he received 196 blood transfusions. He developed extreme brownish pigmentation of the skin due to hæmosiderosis, most likely from transfused blood.[10] Two spontaneous remissions were noted, the latter of nearly a year's duration. Death was due to infection, not to anæmia. Hæmorrhagic features were never noted, presumably as a result of the persistent thrombocytosis attributable to the splenectomy. During the years severe infections such as pneumonia always provoked a considerable granulocyte response. It seems evident therefore that the bone marrow was never aplastic, that it could and did respond in a normal manner if the stimulus was adequate.

The second patient also experienced a spontaneous remission which lasted many months. During this time he looked and felt quite well and the hæmogram was normal. It is of interest that during the first relapse and at autopsy the bone marrow was compact and cellular indicating an anatomically hyperactive tissue though it failed to deliver cells into the circulating blood.

The third patient's illness was characterized by repeated infections. The anæmia and thrombocytopenia were gradual in their onset but rapidly progressive towards the end. The leucocyte formula was nearly always within normal limits though the bone marrow appeared strikingly aplastic in the final stages of the illness. Thrombocytopenia with resulting cerebral hæmorrhages dominated the terminal picture.

DISCUSSION

Etiology.—None of the three patients in this series could be considered to have come in contact with known noxa which may be divided into three groups: (*a*) physical agents such as x-rays or radioactive substances; (*b*) certain drugs and chemical poisons as benzol and its derivatives,[4, 6] gold salts,[7] quinine,[1] iodine[5] and œstrogenic substances;[2, 3, 8] (*c*) pregnancy[12]

FREQUENCY OF OCCURRENCE

Primary aplastic or hypoplastic anæmia is a rare disease in Montreal as the following figures testify. Two previous instances were reported from the Montreal General Hospital in 1931.[13]

Number of autopsies from 1937 to 1945 at Montreal General Hospital	2,535
Number of cases of pernicious anæmia autopsied	12
Other types of primary anæmia autopsied	14
Primary aplastic anæmia	2

The tendency to infections.—The increased tendency to infection is illustrated well by all three patients. Case 1 had pneumonia four times, otitis media and mastoiditis, pericarditis and eventually endocarditis and meningitis. Death was due to infection and not to anæmia. The other two patients suffered from a similar tendency though less severely. This risk is the cause of death in many reported cases although sulfonamides and antibiotics have reduced materially the mortality from infection which no doubt accounts in part for the increased expectancy of life.

The duration of the disease.—The expectancy of life in the idiopathic type of primary idiopathic aplastic anæmia varies within wide limits depending upon the degree of hypoplasia of the marrow. Complete aplasia results in death within a few weeks despite the benefit of unlimited amounts of donor blood. Mild degrees of aplasia are compatible with life for many years. The cases herein reported all fall between these limits as do most of the cases in the literature. The prognosis is obviously influenced by such factors as the ability to call upon an unlimited number of donors, the risks of infection as determined by the patient's age, occupation and social status and the degree to which platelet formation is attacked. A persistent thrombocytopenia results in a hæmorrhagic tendency which is not greatly influenced by transfusions, as illustrated by the case of E.T. The absence of hæmorrhagic phenomena in Case 1 may be attributed to splenectomy which may serve a useful purpose in cases with thrombocytopenia though in no way curative. It should not be considered late in the course of the disease.[9]

Remissions.—Remissions in the disease are not common though they occurred in two of the three cases in this series. The course is nearly always progressively downhill with increasing speed during the descent. This tendency is clearly indicated in the chart illustrating the erythrocyte level and the number of transfusions required in the case of E.T. However, the two younger patients had remissions lasting many months. In the case of B.D. a remission of three months' duration occurred in 1933 after his pneumonia and pericarditis and again in 1943 twelve years after the onset of the disease. On this latter occasion the patient felt quite well and his blood was normal for six months at least. In the case of R.H. the remission lasted nearly a year. In none of these instances could the favourable change have resulted from therapy as the patients were not under specific treatment at the time.

The type of anæmia.—The blood picture in aplastic anæmia is essentially a reduction in the number of marrow cells—erythrocytes, granulocytes and platelets—without such evidence of regeneration as reticulocytes, normoblasts, etc. The erythrocytes, platelets and granulocytes present may be quantitatively reduced but they are qualitatively normal. This does not mean, however, that the marrow is not producing blood cells but rather that it is not producing them at a normal rate. The life of a red cell is probably less than 40 days. Therefore aplastic anæmia of over a month's duration may be hypoplastic anæmia but not complete aplasia. This is true of most clinical cases.

Many eventually show a tendency towards macrocytosis as in 2 of the 3 cases in this report. This fact should be borne in mind if the case is seen late in the course of the disease.

The degree to which the various blood cells are reduced determines the course of the disease. If the reduction in platelets is out of proportion to the reduction in erythrocytes and leucocytes then the hæmorrhagic features predominate—hence the term aleukia hæmorrhagica.[13] If the granulocytes are first wiped out infection is likely to dominate the picture. On the other hand anæmia may be the initial and dominant clinical feature as in one of the three reported patients.

The bone marrow.—The widespread belief that the bone marrow is fatty and devoid of cells in primary aplastic anæmia is not supported by either biopsy or autopsy in two of the three patients and by biopsy of rib marrow in the third. All three showed cellular marrow. In case 1 marrow from the tibia was normal in appearance at a time when his erythrocyte count was slightly over one million. It was histologically hyperplastic eight years later though he had had almost continuous anæmia during the interval and his erythrocyte count was less than half the normal value at the time. The appearance of the marrow is shown in microphotographs 1, 2, 3, and 4.

Case 2 had compact cellular marrow at the beginning of his illness as determined by rib biopsy and erythroblastic hyperplastic areas in

the bones sectioned at autopsy. Microphotographs 5 and 6 illustrate these findings.

In Case 3 the rib marrow was cellular in January, 1945, though the majority of cells were of the myeloid type. In March, 1946, sternal puncture showed red cell aplasia. It seems clear that an acellular fatty marrow is not necessarily a part of the picture in aplastic anæmia.[11] Cell counts done on marrow sections or smears will determine if all types of marrow cells are present and in the proper proportions. It should be recalled that anatomical hyperplasia of the marrow may go hand in hand with functional inefficiency, as in pernicious anæmia in relapse where one finds a grave anæmia in the presence of a very cellular marrow. It is a widespread belief that the most fundamental stimulus to the marrow is a reduction in the blood level of marrow produced cells. Any reduction in their number is at once an urgent demand upon the marrow which may not be denied if the marrow is capable of responding. The problem in aplastic anæmia is whether the marrow is capable of responding or whether an adequate stimulus reaches it. The appearance of the marrow and the fact of spontaneous remissions suggest that it may be the latter.

It is interesting to speculate as to what happens when a remission occurs and also as to the nature of mechanism which brings this about. Do the areas of actively functioning marrow suddenly become more efficient or does a greater area of bone marrow spring into activity? In pernicious anæmia in relapse, for example, all the marrow is cellular and active in appearance yet few cells are delivered to the circulating blood until the erythrocyte maturing factor (E.M.F.) from the liver is supplied in normal quantities. But the E.M.F. is inert in the matter of producing a remission in aplastic anæmia. From the fact that remissions do occur at intervals—even after some years—as in the case of B.D., it may be argued that the marrow is potentially active and normal requiring only an adequate stimulus to cause it to spring into activity. Blood loss or depletion is ordinarily regarded as the adequate stimulus to the bone marrow. This is obviously not the case in aplastic anæmia. The marrow is ready to produce blood in adequate amounts, the circulating blood is impoverished of one or more types of marrow produced cells and yet the marrow remains functionally hypoplastic. It would seem logical to conclude that there exists, in addition to the E.M.F., deficient in pernicious anæmia, a second substance which controls the rate of blood formation — which exerts some type of quantitative control over blood formation—and that this factor is absent or depleted in primary aplastic anæmia.

SUMMARY AND CONCLUSIONS

Three cases of idiopathic aplastic or hypoplastic anæmia are reported. All three presented interesting variants from the generally accepted pattern of the disease.

The bone marrow in hypoplastic anæmia frequently proves to be compact and cellular, not fatty and aplastic.

Remissions of the disease may occur even after a period of twelve years.

Transfusions may be the means of tiding the patient over long periods of relapse in the expectation of a prolonged remission. It is suggested that the bone marrow in this disease is potentially normal requiring only some adequate stimulus to restore normal function. The nature of this regulating mechanism is not known.

REFERENCES

1. CUSTER, R. P.: *Am. J. M. Sc.*, **212**: 211, 1946.
2. MACKAY, R. P. AND GOTTSTEIN, W. K.: *J. Am. M. Ass.*, **132**: 13, 1946.
3. HARRISON, F. H., JOHNSON, R. D. AND AYER, D.: *J. Am. M. Ass.*, **132**: 11, 1946.
4. SIEVERS, R. F., STUMP, R. L. AND MONACO, A. R.: *Occup. Med. J.*, **1**: 351, 1946.
5. BOUSSER, J. AND HUGUET, S.: *Sang*, **16**: 191, 1944.
6. BÉNARD, R., POUMAILLOUX, M. AND TIRET, J.: *Sang*, **15**: 351, 1943.
7. PERGOLA, A.: *Sang*, **16**: 37, 1944.
8. CHEVALLIER, P. AND UMDENSTOCK, R.: *Sang*, **15**: 528, 1943.
9. SHAW, M. AND OLIVER, L. C.: *Proc. Roy. Soc. Med.*, **38**: 479, 1945.
10. BETHELL, F. H., STURGIS, C. C., RUNDLES, R. W. AND MEYERS, M. C.: *Arch. Int. Med.*, **76**: 379, 1945.
11. PEARCE, R. S.: *Memphis M. J.*, **19**: 51, 1944.
12. BIGBY, M. A. M. AND JONES, F. A.: *J. Obst. & Gyn. Brit. Emp.*, **53**: 182, 1946.
13. MILLS, E. S.: *Am. J. M. Sc.*, **521**: 181, 1931.

A FORGOTTEN TOURNIQUET—The governors of the Oldham Royal Infirmary admitted liability in a claim by a widow at Manchester Assizes on March 17 for damages for the death of her husband aged 53. He had fractured his wrist at work in November, 1944, and a bone graft became necessary. A graft was taken from his shin on October 4, 1945, and eleven hours after the operation, although he had been in great pain for a long time, someone discovered that the tourniquet round his thigh had not been removed. Even then further delay took place before a surgeon was called to give him a blood transfusion, and he died next day. Counsel said that there was no system by which tourniquets were checked. Mr. Justice Singleton awarded £4,000 damages and costs.—*Brit. M. J.*, April 12, 1947.

HYPERPARATHYROIDISM

Geo. H. Stobie, M.D., F.R.C.S.[C.], F.A.C.S.

Belleville, Ont.

THE clinical entity known as hyperparathyroidism, which has been developed and brought to its present well understood state within the past twenty years, constitutes one of the recent triumphs of medical science. The parathyroid glands were not discovered until 1880, and not until 1904 did Askanazy associate a parathyroid tumour with skeletal lesions. In 1925 Mandl, a Viennese surgeon, first removed a parathyroid adenoma and cured a case of hyperparathyroidism. Coincident with this event, Collip discovered the parathyroid hormone (parathormone) and was able to produce hyperparathyroidism by injecting this hormone into patients and animals. This definitely proved it to be a hyperfunctioning, endocrine glandular disease.

In the study of medicine, a rare condition is made less rare and more significant clinically only when attention is called to it and one's diagnostic acumen becomes keener as the threshold of suspicion rises. Up until 1942, only 14 cases of hyperparathyroidism due to a parathyroid adenoma had been recognized at the Mayo Clinic; within the next two years 24 proved cases were seen. Aelxander *et al.*[1] state that this apparent increase in incidence was due to the fact they were on the lookout for it since they understood its symptoms better. Hyperparathyroidism is still a rare disease. There are only 322 cases reported in literature. An excellent collective review of these cases has been made by Norris[2] in which he makes a request that all cases of hyperparathyroidism be reported for at least the next ten years.

My reason for reporting this case is to show the complete recovery of a well advanced case, with marked bone changes, seven years after the removal of an adenoma; and to give a short review of some of the excellent articles that have been published recently in order to again bring this disease to the attention of the profession, in the hope that it will be recognized more often in its early stages before irreparable deformities have occurred. It has been well illustrated by Albright *et al.*[3] at the Massachusetts General, where they have had the greatest number of cases of any clinic, that this is a disease which can be detected early, as they did with many of their 75 reported cases.

Hyperparathyroidism may be either primary or secondary. Primary; when it arises in response to known stimulus or physiological need of the body. Secondary; when it results from physiological need, such as in severe and long-standing renal insufficiency, rickets, pregnancy and osteomalacia.

Primary hyperparathyroidism has been shown in the data collected from these 322 cases, to have been caused in 90% of the cases by a hyperfunctioning adenoma of one or more parathyroid glands; and in 10% of the cases, it was caused by a diffuse hyperplasia or hypertrophy of all the parathyroid tissue as reported by Cope[4] and more recently by Black and Sprague[5] of the Mayo Clinic.

It is well understood now that the calcium metabolism of the body is governed by the parathyroid glands. Normally the blood serum contains from 9.5 to 11.5 mgm. of Ca. per 100 c.c. (Schelling). The serum value of phosphorus is 3.5 $\pm$ 0.05 mgm. per 100 c.c. (Azpuru). When a hyperactive parathyroid condition develops, or when it is produced experimentally by injecting parathormone, the calcium is taken from the bones and excreted by the urine. A state of hyperparathyroidism is diagnosed when the serum calcium level reaches a concentration above 12.5 mgm. per 100 c.c. It has been found as high as 29 mgm. per 100 c.c. Accompanying this hypercalcæmia a state of hypophosphotæmia is always found. It may be as low as 1.5 mgm. per 100 c.c.

Hyperparathyroidism is a disease that runs usually a slow progressive course and has been known to exist for as long as 39 years, but usually is present on an average from 5 to 7 years before being detected. It is subject to remissions when the bones may become partially remineralized and it has been known to completely subside and the bones return to normal. Occasionally it runs a rapid, fulminating course and ends fatally due to parathyroid poisoning. It has been observed in people ranging in age from 10 to 77 years, but 70% of the cases were observed in the range from 30 to 60 years of age. It is three times more common in women than in men. It has no geographical distribution.

DIAGNOSIS

Most cases of hyperparathyroidism that have been diagnosed are late cases with marked skeletal involvement or cases with kidney complications resulting from long standing hyperparathyroidism. Unfortunately these two late manifestations have come to be regarded as inevitable requirements in making a diagnosis. But Albright[3] and his co-workers at the Massachusetts General Hospital, who have been pioneers in this work and have now reported over 75 cases, as well as Keating[6] at the Mayo Clinic, have shown that a large percentage of their cases showed no skeletal involvement or very minimal involvement. Likewise only a small percentage showed genito-urinary complications and it was possible to diagnose hyperparathyroidism without either of these late findings.

The clinical manifestations of primary hyperparathyroidism vary a great deal from patient to patient. Albright[3] divided the symptoms into three groups: (1) symptoms produced by the chemical changes in the blood *per se*; (2) symptoms produced by involvement of the urinary tract; (3) symptoms produced by involvement of the skeleton.

The symptoms of increased calcium are muscular atony, weakness, fatigue, constipation, anorexia, loss of weight, nausea and vomiting, polydipsia and polyuria which are exactly the opposite to those found with a decreased calcium.

Symptoms produced by the involvement of the urinary tract may be due entirely to the chemical change in the urine *per se*. Hypercalcinuria as high as 8 times the normal amount has been recorded in uncomplicated primary hyperparathyroidism as well as hyperphosphaturia. Calcium is hard to keep in solution and therefore large quantities of water must be taken. This explains the symptoms of polydipsia and polyuria which often lead to the erroneous diagnosis of diabetes insipidus. In a large number of these cases, the excessive amount of calcium passing through the kidney sooner or later forms calculi either in the pelvis or papillæ and are usually of the calcium oxalate type. Keating[6] found stones in 19 out of 24 cases. Also a condition known as nephrocalcinosis occurs where the calcium becomes deposited in the tubules. This leads to marked destruction of renal substance and serious renal insufficiency. This is quite the most serious complication of hyperparathyroidism because it is irreversible.

Symptoms resulting from involvement of skeleton. Any degree of demineralization may exist from a very slight degree, where there are minor aches and pains present, to a degree known as osteitis fibrosa generalisata where the bones become so soft that deformities occur such as kyphosis and lordosis. Patients have been known to lose several inches in height as a result of this. The legs are bowed, the pelvis becomes deformed, spontaneous fractures occur especially in the long bones and ribs. The skeletal findings are generalized and never localized, which distinguishes it from other diseases such as Paget's which may be confused with it roentgenologically. The more marked the bony involvement, the more pain is experienced along the bones and joints, and localized painful swellings may occur in the region of bone cysts.

Any or all of the above symptoms may be present in this disease, but more often some symptoms are more pronounced than others, and depending on what system is most affected determines what specialist is consulted first. Chapman[7] has pointed out that the dentist may be consulted first on account of bad teeth or maxillary or mandibular cysts which are very common. Pain in the præcordium is common and the cardiologist is often consulted; likewise the neurologist, on account of nerve root pressure from deformity of the spine; the orthopædist on account of bone and joint pains and spontaneous fractures; the internist on account of secondary anæmia, muscular weakness, nausea and vomiting and dysentery; the urologist of course, sees a large percentage. Alexander *et al.*[3] gave a list of the first impression physicians had of these patients when they were first examined: (1) renal colic; (2) sciatic neuritis; (3) chronic glomerulonephritis; (4) nutritional deficiency with anæmia and osteoporosis; (5) menopausal osteoporosis; (6) anorexia nervosa; (7) chronic infectious arthritis; (8) osteomyelitis and (9) bone tumour.

Thus it will be seen how protean and variable primary hyperparathyroidism is in its clinical manifestations.

Keating Jr.[6] stated that hyperparathyroidism should be suspected in (1) all cases of renal stones—especially when bi-lateral—in young individuals where no infection, obstruction or other causes could be found; (2) where a generalized decalcification of the bone existed; (3)

all cysts or bone tumours; and (4) where polydipsia or polyuria is present. The diagnosis can only be confirmed by laboratory findings.

DIFFERENTIAL DIAGNOSIS

Hyperparathyroidism must be differentiated from other conditions that produce hypercalcæmia, hypophosphatæmia, hypercalcinuria, and osteoporosis. The use of massive doses of vitaman D has become quite popular in the treatment of arthritis during the past few years, and the fact that primary hyperparathyroidism can mimic the symptoms of chronic arthritis very closely, coupled with the fact that hypervitaminosis D can produce hypercalcæmia, hypophosphatæmia and hypercalcinuria and also generalized osteoporosis, makes it necessary to always enquire if a patient has been on this treatment and if so, sufficient time must be allowed to elapse after treatment has been discontinued so as to get a blood chemistry finding that is not influenced by the effect of excess vitamin D.

Compensatory hyperparathyroidism may be caused by chronic renal insufficiency and is considered to be the cause of renal rickets in children, renal osteitis fibrosa cystica in adults and has been suggested as the cause of the generalized demineralization found in multiple myeloma and metastatic tumours of bone. It has been pointed out by Keating[6] that the differential diagnosis between primary hyperparathyroidism with osteitis fibrosa cystica and renal osteitis fibrosa cystica second to urinary insufficiency caused by primary renal disease with accompanying secondary hyperparathyroidism is of more than academic interest, because in the primary condition, if the adenoma be removed, life will be prolonged whereas in the second condition, life will probably be shortened if surgery is resorted to.

Conditions that produce generalized or local bone changes that may be confused with the bone changes found in primary hyperparathyroidism are: (1) post menopausal or senile osteoporosis; (2) generalized carcinomatosis; (3) multiple myeloma; (4) osteoporosis of hyperthyroidism; (5) osteomalacia. A careful interpretation of the clinical features and chemical findings of the blood will clarify the diagnosis in these cases.

There are several localized diseases of bone that may be confused with the cystic changes found in the bones in primary hyperparathyroidism: (1) Paget's disease or osteitis deformans often resembles the bone changes found in hyperparathyroidism. These two diseases as pointed out by Gutman and Parons[8] are quite different but are often co-existent and this makes the diagnosis extremely difficult. (2) Polyostotic fibrosis dyplasia is another condition which resembles the bone changes of hyperparathyroidism very closely but is found to be unilateral. Garlock[9] wrote an excellent article on the differential diagnosis of this condition and recently Coleman[10] reported a case.

Hyperparathyroidism is a metabolic disease producing generalized bone changes. Therefore if one area of normal bone is found in a patient with otherwise widespread pathological changes, the diagnosis of hyperparathyroidism can be ruled out. If on repeated blood examination, hypercalcæmia, hypophosphatæmia and hypercalcinuria are found to exist in a patient with clinical findings resembling hyperparathyroidism, who has adequate kidney function, one is justified in recommending that the parathyroids be explored and this can be done in the absence of bone and kidney changes.

If this disease is to be diagnosed more often, more frequent blood calcium estimations will have to be made when patients complain of generalized aches and pains, especially when root nerve pressure symptoms are present and in patients with urinary calculi.

TREATMENT

No form of treatment, including heavy radiation, has been of value in this condition except surgical ablation of the adenoma or removal of all the hyperplastic tissue except 250 mgm. (Black and Sprague[5]). When all the hyperactive tissue has been found and removed, cure is evidenced by a return to normal of the blood chemistry, remineralization of the bones and a disappearance of the clinical symptoms. When these criteria are not fulfilled after operation, there is always the question whether it was a faulty diagnosis or failure to find the adenoma.

Normally there are two parathyroid glands on either side behind the thyroid lobes but there are many developmental defects and displacements. These are dealt with in a splendid article by Gordon-Taylor and Handley[11] and more recently by Azuru and Black[12] of the Mayo Clinic, in which they report a case where the adenoma was found in the mediastinum.

This article also mentions the very excellent way the surgeon can be led to find an adenoma in the mediastinum by exploring the inferior thyroid artery and following any branch that may descend into the mediastinum, or into the areolar tissue behind the clavicle, a method advocated by Lahey.[14] Lahey also advised exploration of the posterior part of the superior pole of the thyroid gland; after cutting the superior thyroid artery and vein, the upper parathyroid gland with a tumour has been found imbedded in the thyroid tissue there on several occasions; 6% of adenomas are found in aberrant positions. The posterior fascia must be opened and the area behind the œsophagus explored before search for adenomatous tissue is abandoned. Norris's[2] review showed the adenoma to occur almost equally in the right and left lower parathyroids. The size of the adenoma bears no relation to the severity of the symptoms. Hunter[13] reported a case of a woman 37 years of age who after four years of total crippledom, including great bone deformities and destruction of hip joints and shoulder joints, had a tumour weighing only 1.3 gm. removed and soon walked with sticks.

Postoperative Course

The calcium content of the blood has been found to drop very suddenly to dangerous levels after the removal of the adenoma in patients who showed a great deal of bone disease. If the calcium level drops below 8 mgm. per 100 c.c., tetany often occurs. This sudden drop is not observed in patients who do not show much osseous change. The amount of bone destruction may be determined by the amount of phosphatase, an enzyme which is released when there is active bone destruction and can be estimated in the urine. The normal value is 3 to 5 Bodansky units but this may increase to 20 in severe cases. This enzyme is not indicative of hyperparathyroidism alone but is found in other malacic states. Postoperative hypocalcæmia must be combated with high calcium intake and the administration of parathormone for some time following operation. Lahey[14] thinks that the sudden fall in calcium level is due to the fact that all the work of producing parathormone has been done by the hyperactive adenoma and that the normal parathyroid glands have become inert and it takes them some time to resume their normal function after operation.

Case Report

G.G., male, aged 17 was admitted May 18, 1940 with a supracondylar fracture of his right humerus caused by a very slight amount of trauma. He gave a history of a fracture of the left wrist two years previously with a similar slight injury. He also gave a history of having a tumour removed from his jaw in the Toronto Western Hospital two years previously. Reports from this hospital reported a giant-celled tumour having been removed there. Family history was not significant. This boy had always been submental and backward. He was tall, very stooped and anæmic-looking. X-ray examination revealed a fracture of the lower end of the right humerus through a fibro-cystic area (Fig. 1). This with the history of a previous fracture and the giant-celled tumour having been removed from the jaw led to further investigation, which disclosed generalized osteoporosis and other fibro-cystic areas. Fig 2 shows the condition of the skull.

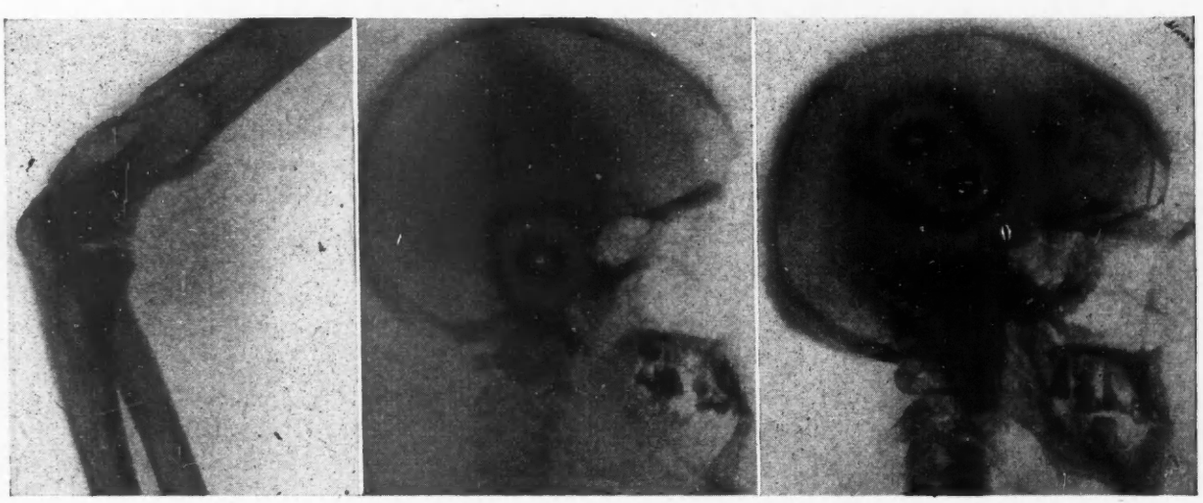


Fig. 1 Fig. 2 Fig. 3

Fig. 1.—Fracture through fibro-cystic area of lower humerus. Serum calcium 13.6 mgm. %; serum phosphorus 1.5 mgm. %. **Fig. 2.**—Skull on admission, showing marked osteoporosis. Serum calcium 13.6 mgm. %; serum phosphorus 1.5 mgm. %. **Fig. 3.**—Seven years following operation—bones completely remineralized. Serum calcium 11.1 mgm. %; serum phosphorus 3.8 mgm %; phosphatase 5.4 units.

Blood examination: Serum calcium 13.5 mgm. per 100 c.c.; serum phosphorus 1.5 mgm. per 100 c.c.; red blood cells 5,200,000; Hb 88.2%; white blood cells 11,400. This confirmed the diagnosis of hyperparathyroidism.

The arm was adequately splinted and on June 11, 1940, the parathyroid glands were exposed. The right side was examined first but no tumour was found. Then the left side was examined and a plum-coloured tumour was found replacing the left lower gland quite close to the clavicle. It was easily removed. It measured 2.5 x 1.5 x 0.3 cm. Convalescence was uneventful and rapid. No symptoms of tetany were seen. The pathological diagnosis was parathyroid adenoma (chief cell type).

Blood serum calcium on June 26, 1940 was 11.6 mgm. per 100 c.c. By July 6, 1940 the calcium level had fallen to 9.7 gm. per c.c. and the phosphorus value was 1.4 mg. per 100 c.c. at this time. On August 27, 1940, the calcium level had risen to 10.4 mgm. per 100 c.c.

He was discharged on July 11, 1940 with good bony union of his humerus but still with a protective cast. He returned home to the farm. His mental calibre was that of a child of six. Two years ago he became violent and had to be incarcerated in a mental hospital. Through the kindness of Dr. J. S. Stewart, Superintendent of the Ontario Hospital at Kingston, the present blood chemistry was obtained and also a series of x-ray pictures of his skeleton. Fig. 3 shows the remineralization of the skull seven years after operation.

February 26, 1947: The serum calcium was 11.1 mgm. per 100 c.c.; serum phosphorus 3.8 mgm. per 100 c.c.; serum alkaline phosphatase 5.4 units.

His general condition at present is normal and has had no more bony injuries but his mental condition remains the same.

I wish to thank Prof. W. L. Robinson for the pathological report on this case, also Dr. Sleman of the Toronto Western Hospital for a report on the clinical and pathological work done there, and also Dr. J. S. Stewart, Superintendent of the Ontario Hospital, Rockwood, for furnishing me with the present blood findings and x-rays.

REFERENCES

1. ALEXANDER, H. B. *et al.*: *Am. J. Surg.*, **65**: 157, 1944.
2. NORRIS, E. H.: *Surg., Gyn. & Obst.*, **84**: 1, 1947.
3. ALBRIGHT, F. *et al.*: *Arch. Int. Med.*, **62**: 199, 1938. ALBRIGHT, F., SULKOWITCH, N. W. AND BLOOMBERG, E.: *Am. J. M. Sc.*, **193**: 800, 1937.
4. COPE, O.: *Surgery*, **16**: 273, 1944.
5. BLACK, B. M. AND SPRAGUE, R. G.: *Proc. Mayo Clin.*, **22**: 73, 1947.
6. KEATING, F. R., JR.: *Med. Clin. N. Am.*, p. 1019, July, 1945.
   Idem: *J. Mich. State Med. Soc.*, **45**: 1349, 1946.
7. CHAPMAN, H. S.: *West. J. Surg., Obst. & Gyn.*, July, 1941.
8. GUTMAN, A. B. AND PARSONS, W. B.: *Ann. Int. Med.*, **12**: 13, 1938.
9. GARLOCK, J. H.: *Ann. Surg.*, **108**: 347, 1938.
10. COLEMAN, H. M.: *Canad. M. A. J.*, **56**: 316, 1947.
11. GORDON-TAYLOR, G. AND HANDLEY, R. S.: *Brit. J. Surg.*, **25**: 6, 1937.
12. AZPURU, C. E. AND BLACK, B. M.: *Proc. Staff Meet. Mayo Clin.*, **22**: 57, 1947.
13. HUNTER, D.: *Brit. M. J.*, **1**: 982, 1937. *Idem*: *Med. Press*, **204**: 432, 1940.
14. LAHEY, F.: *Ann. Surg.*, **121**: 454, 1945.

The ideal of medicine is the prevention rather than the cure of disease, and for this end the detection of the earliest stages, and better of the disposing causes of diseases, is essential. Timely warning about diet, exercise and manner of life may do much to prevent disease from getting a firm seat on a man's back.—Aspects of Age, Life and Disease, Sir H. Rolleston, p. 14, 1928.

CONGENITAL ŒSOPHAGEAL ATRESIA

(Some Anatomical and Embryological Aspects)

R. L. deC. H. Saunders, M.D., F.R.S.E.

Halifax, N.S.

and

H. S. Wright, M.D.

Fredericton, N.B.

UNTIL relatively recently congenital œsophageal atresia was regarded as a rare and hopeless condition, incapable of treatment other than by gastrostomy. Interest in the malformation, together with improved diagnostic procedures has led not only to its more frequent detection, but also to marked progress in its surgical management. End-to-end anastomosis of the œsophageal segments, conducted extrapleurally, with ligation of a tracheo-œsophageal fistula if present, is regarded as the surgical ideal, and although unfortunately not always possible has been carried out successfully in a large number of cases.

The clinician most frequently meets with that type in which the upper part of the œsophagus ends in a blind pouch, while the lower part communicates by a tracheo-œsophageal fistula with the respiratory passages. Although the clinical aspects of such cases have been described, it seems necessary to draw attention to the anatomical features of each new case in the cause of improved surgical technique. The following case is presented therefore with the object of stressing the possibility of encountering vascular anomalies in the region of the defect, and encouraging interest in the disposition of the nerves in the operative field.

CASE REPORT

A two-day old baby, was admitted to hospital with a pre-admission diagnosis of imperforate anus. On admission meconium was observed passing through the vulva and a diagnosis of persistent cloaca or fistula was made.

Regular feeds were commenced but the child regurgitated all feeds immediately. In view of this it was given a little barium and x-rayed. The bolus of barium came to an abrupt stop just below the clavicles at about the level of the third thoracic vertebra, indicating a congenital œsophageal atresia.

Hypodermoclysis was instituted and a gastrostomy carried out next day. Feedings were then started through the tube, but were immediately followed by coughing and cyanosis, with regurgitation of the feed through the nose and mouth. Introduction of a little barium into the gastrostomy tube under the fluoroscope caused a repetition of these phenomena and led to the assumption that the œsophagus communicated with a bronchus.

The next day the baby was very cyanosed, with a rapid respiratory rate, and died during the day. A routine autopsy revealed a cloaca, apparent absence of the uterus, œsophageal atresia, and a tracheo-œsophageal fistula. Following on this the viscera were forwarded to one of us (R.L.S.) for more careful dissection than is generally possible during an autopsy.

Anatomical findings.—Dissection revealed that the œsophagus terminated bulbously in a blind pouch 2.3 cm. below the level of the cricoid, and 1.7 cm. above the tracheal bifurcation; in its fixed state it was 9 mm. in diameter and approximately 27 mm. in circumference. Loose connective tissue connected the anterior aspect of this pouch with the trachealis muscle on the posterior aspect of the trachea.

Immediately below this pouch was some fat, lymph glands, and connective tissue, and an aberrant right subclavian artery (Fig. 1). Below this again was the tracheal bifurcation and the lower œsophageal segment.

The lower or infratracheal segment of the œsophagus in its fixed state measured 5 cm. from the cardiac orifice of the stomach to a point just above the tracheal bifurcation (6 mm. above the carina) where it communicated fistulously with the posterior aspect of the trachea. This lower part of the œsophagus ranged from 6 mm. in diameter at its lower end to 5 mm. at its upper end. Its opening into the trachea was 3 mm. wide and was guarded inferiorly by a crescentic lip.

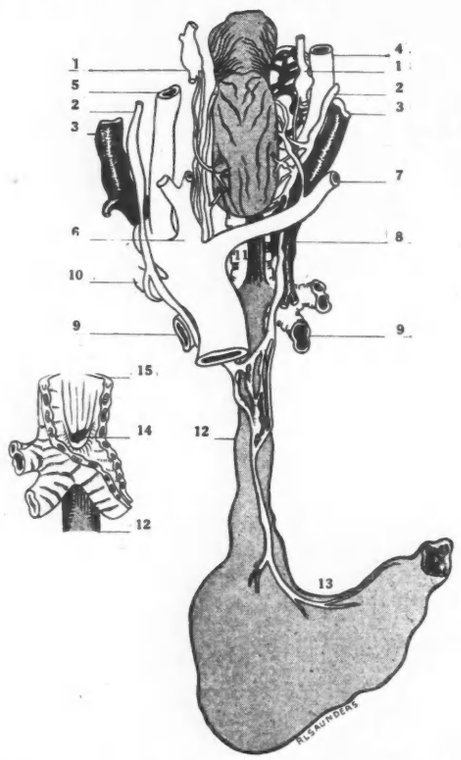


Fig. 1.—Posterior view of trachea to show the retrotracheal œsophageal pouch, and the communication between the infra-tracheal œsophageal segment and the trachea. Inset shows anterior view of this communication or fistula.

1, 1. Right and left sympathetic trunk; former rests on right thyroid lobe.
2. 2. Right and left vagus nerve.
3, 3. Right and left innominate vein.
4. Right common carotid artery.
5. Left common carotid artery.
6. Left subclavian artery.
7. Right subclavian artery.
8. Vena azygos.
9, 9. Right and left bronchus.
10. Ductus arteriosus; left recurrent nerve.
11. Band between fistula and pouch.
12. Infra-tracheal œsophageal segment.
13. Stomach and post. gastric nerve.
14. Tracheo-œsophageal fistula.
15. Trachea laid open.

Removal of the tissue just below the retrotracheal segment or pouch of the œsophagus, with displacement of the aberrant artery, revealed the presence of a network of small veins or venous collar connecting the azygos and hemiazygos systems of veins. In addition it showed that a distinct band of muscular tissue, 2 mm. broad and 1.6 cm. long, extended from the site of the fistula up to the anterior aspect of the retrotracheal pouch which it joined 4 mm. above its blind tip. This band of muscle tissue was not patent, and was fused with the trachealis muscle of the trachea; it was apparently the representative of the ablated portion of the œsophagus.

The general relationships of the retrotracheal pouch may be gathered from Fig. 1. It will be noticed that the right subclavian artery arose caudal to the left subclavian as the last trunk of the aortic arch. Crossing immediately below the retrotracheal œsophageal pouch it then ascended somewhat lateral to the pouch to attain the right arm. As it did so, the right subclavian gave off the inferior thyroid artery, which passed upward on the right lateral aspect of the pouch to reach the inferior pole of the thyroid gland.

The right vagus nerve descended lateral to the pouch and gave a very marked contribution to it. Its right recurrent branch passed directly to the larynx but also supplied the pouch. The left vagus did not appear to contribute to the pouch, although its recurrent branch supplied both the pouch and the trachealis muscle. Both vagi united on the infratracheal œsophageal segment a short distance below the tracheal bifurcation in order to form the œsophageal plexus.

The sympathetic trunks had unfortunately been cut at autopsy, but sufficient remained to note that the left sympathetic trunk supplied a number of branches to the left side of the pouch. Fewer sympathetic branches were observed on the right side. It is regretted that no further statement can be made regarding the identity of the ganglia which contributed to the pouch.

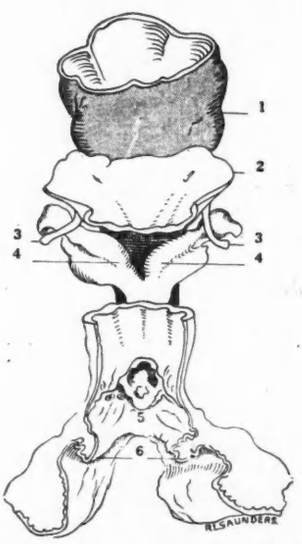


Fig. 2.—Anterior view of the pelvic viscera following removal of the anterior part of the urinary bladder, and transection of its posterior wall.

1. Rectum.
2. Base of urinary bladder.
3, 3. Right and left ureter.
4, 4. Right and left horn of bicornuate uterus.
5. Cervix. Note small cervical and large rectal orifice above the figure.
6. Labia minora.

The state of the pelvic viscera may be best gained from Fig. 2. The rectum opened by a fistulous orifice 3 mm. wide into a cloacal chamber, which was bounded inferiorly by the labia minora, and superiorly continuous with the urinary bladder. Just below the rectal orifice was a crescentic, imperfectly formed cervix with an

opening on its upper aspect suggestive of an external os. Transection and reflection of the posterior wall of the urinary bladder revealed a uterus bicornuis, whose two horns fused partially in front of the rectum and then swept on either side of its fistulous orifice to end in the poorly formed cervix.

Embryological aspects.—In congenital œsophageal atresia the œsophagus, either in whole or part, undergoes a developmental ablation or interruption. Various types are encountered and Vogt's[1] classification is now used by most clinicians.

Type 1 or complete agenesia of the œsophagus is rare. In type 2 there is a partial ablation of the œsophagus. The upper or retrotracheal segment ends in a blind pouch and this may or may not be connected by a fibrous or muscular band with the blind proximal end of the lower or infratracheal œsophageal segment. Types 3a and 3b are characterized by the presence of a tracheo-œsophageal fistula. In the former this involves the retrotracheal œsophageal segment, while in the latter it connects the infratracheal segment with either the trachea or a bronchus. This last type which is illustrated by the present case is the most often encountered in practice. Fistulæ connecting both retro- and infratracheal œsophageal segments with the trachea constitute type 3c.

Congenital œsophageal atresia has been attributed to various factors but the ultimate agents responsible are not known. Pressure atrophy due to abnormal vessels and faulty œsophageal canalization have both been suggested as causal factors but neither will stand embryological scrutiny.

The most widely accepted theory is that of imperfect formation or deviation of the tracheo-œsophageal septum. Following the outgrowth of the lung bud, subdivision of the foregut into its tracheal and œsophageal parts is usually visualized as being brought about by the ingrowth of two laterally placed septa. Tracheo-œsophageal fistulæ are ascribed to a failure of fusion of these septa. The atresia is commonly regarded as being due to a dorsal deviation or undue obliquity of these selfsame septa which thus subdivide the œsophagus into upper and lower segments. Incidentally, the fusion of the septa is often erroneously described as proceeding caudally; contrary to developmental rule it proceeds cephalically.[2]

All the types described can be explained on such a basis but it is at best a plausible explanation of the developmental history and does not bring us much nearer to an understanding of the formal genesis of the condition.

Neither the dual origin of the retro- and infra-tracheal portions of the œsophagus, nor the differential rate of growth and œsophageal elongation which attend pulmonary development seem to have received the attention which they appear to merit. Until more trustworthy evidence is forthcoming, Rosenthal's[3] interpretation of the morphogenesis as an altered or deficient cell growth resting possibly on a genetic basis is perhaps as far as the subject of its etiology can be pursued. In the light of this, attention might be drawn to MacKenzie's[4] case in which a man fathered three children by three different mothers, and each child had an œsophageal atresia.

As regards the abnormal right subclavian artery it would appear that the fourth right aortic arch and cephalic part of the right dorsal aorta were obliterated, with the result that the portion of the artery below the œsophageal pouch must have arisen from the caudal part of the right dorsal aorta. Cephalad migration of the right and left subclavians on the aortic stem to a point immediately above the site of the ductus arteriosus would explain their adjacent origin from the aortic arch.[5] An abnormal right subclavian artery usually has a lower origin, and as a rule arises from the descending aorta.

This artery is of interest in that all three of the cases of œsophageal atresia described by Keith[6] had an abnormal subclavian artery traversing the interval between the upper and lower œsophageal segments. In two of his cases there was a right aortic arch and an abnormal left subclavian passed below the œsophageal pouch, while the conditions in the third case were similar to those described here.

The pelvic anomaly would appear to have arisen as a result of the caudally extending Mullerian ducts having encompassed a fistula that united the rectum and urogenital sinus, with the result that the rectum appeared to open into the cervical part of the bicornuate uterus.

DISCUSSION

Operative experience has shown that the anomalous structures in congenital œsophageal atresia are most easily and safely reached by a right-sided extrapleural exposure.[7] The risk of encountering an abnormal right subclavian

artery, and a low inferior thyroid artery arising from it, are therefore points worthy of surgical consideration.

Fortunately, however, it appears possible to detect the presence of an abnormal right subclavian artery in the radiograph. The fact that the normal left subclavian artery is sometimes visible in an antero-posterior chest film led to an inspection of the films of this case to see whether or not an abnormal right subclavian artery might be detected. This revealed a curved shadow passing from the mediastinal shadow across the apex of the right lung toward the posterior part of the first rib in a manner agreeing with the position of the abnormal right subclavian artery as found at dissection.

An additional point of surgical interest is the marked contribution of the right vagus to the retro-œsophageal pouch, since the mobilization of the pouch necessary to effect an anastomosis may result in damage to these vagal branches with possibly postoperative repercussion.

We are indebted to Dr. H. C. Reardon for clinical notes and Dr. J. S. Hynes and Dr. R. L. Smith for radiological particulars.

REFERENCES

1. VOGT, E. C.: *Am. J. Roentgenol.*, 22: 463, 1929.
2. AREY, L. B.: Developmental Anatomy, 2nd ed., W. B. Saunders Co., p. 210, 1932.
3. ROSENTHAL, A. H.: *Arch. Path.*, 12: 756, 1931.
4. MCKENZIE, M., cited by Singleton, A. O. and Knight, M. D.: *Ann. Surg.*, 119: 556, 1944.
5. DOLGOPOL, V. B.: *J. Tech. Methods*, 13: 112, 1934.
6. KEITH, A. AND SPICER, J. E.: *J. Anat.*, 41: 52, 1906-07.
7. HOLT, J. F., HAIGHT, C. AND HODGES, F. J.: *Radiology*, 47: 457, 1946.

Dalhousie University.

PRIMARY CARCINOMA OF THE URETER*

Frederick Pilcher, M.D., M.Sc.

Calgary, Alta.

THE ureter is an uncommon site for primary carcinoma. This lesion is a cause for hæmaturia however and must be kept in mind because its diagnosis is not always easy, as is illustrated by one of the cases reported here. The numerous case reports in recent years suggest that this disorder is not so rare as was once thought. Attention has been drawn to it by many reports in the literature and modern diagnostic technique makes its clinical recognition less difficult than formerly.

The first case of primary carcinoma of the ureter was reported by Rayer[5] in 1841. The tumour was discovered at autopsy and the diagnosis based on gross rather than on microscopic examination. In 1878 Wising and Blix[8] reported the first case complete with microscopic diagnosis. Since that time many individual cases have been reported and a number of rather extensive reviews of the literature have been made.[1, 2, 4, 7] The reported cases now total approximately two hundred.

CASE 1

Mr. A.W.B., aged 56, was referred to our clinic on March 9, 1938, on account of hæmaturia. Approximately six weeks previously he had developed a pain in the right loin and right side of the abdomen, accompanied by leucocytosis and normal urine. It was thought that he had appendicitis and the appendix was removed. Urinalysis during convalescence was negative. About four weeks after the appendix operation his pain recurred and this time it was accompanied by gross hæmaturia. An excretory urogram showed no dye in the right kidney and the patient was sent to us for further examination.

An excretory urogram made by us on March 9, showed a normal left kidney and no dye appeared on the right in any of the films. Cystoscopy in the office showed a small tumour projecting from the ureteral orifice. The patient was sent to the hospital where cystoscopy was repeated under sacral block anæsthesia on the following day. The tumour protruding from the right ureteral orifice was removed with forceps. A catheter was then passed up the right ureter and met with an impassable obstruction about 4 cm. from the ureteral orifice. Dye was injected and a ureterogram made (Fig. 1). This showed a filling defect which was thought to be either a primary tumour of the ureter or an extension down the ureter of a primary tumour of the renal pelvis.

On March 12, under spinal anæsthesia the right kidney was exposed through the usual flank incision. It was found to be a thin shell filled with about 900 c.c. of urine and old blood. The ureter was tremendously dilated. Palpation of the ureter showed a tumour mass in the ureter at about the brim of the pelvis. The ureter was clamped, cut and ligated above this mass and the kidney removed. The kidney was a mere hydronephrotic shell and the mucosa of the pelvis and upper ureter was entirely free from tumour. Convalescence was uneventful.

Thirteen days later, on March 25, 1938, under spinal anæsthesia the right ureter was exposed extraperitoneally through a Gibson incision. The entire ureter was removed and with it a circular piece of bladder wall and mucosa surrounding the ureteral orifice about 3 cm. in diameter. The opening in the bladder was closed in two layers and a catheter placed in the urethra for drainage. Convalescence was uneventful. Microscopic examination of the tumour was made by Dr. A. C. Broders who reported it a grade 2 carcinoma.

Follow-up cystoscopy on August 6, 1938 and January 19, 1939, showed no tumour in the bladder. On November 20, 1939, cystoscopy revealed two small papillomas in the base and posterior wall of the bladder. These were destroyed in the office by electrocoagulation. Cystoscopy again on May 20, 1946, showed no further recurrence and abdominal examination revealed no suspicion of metastases.

CASE 2

Mr. C.H.D., aged 58, was referred to our clinic on June 4, 1940, on account of hæmaturia one year previously and another approximately two weeks before the

* Read at the Seventy-seventh Annual Meeting of the Canadian Medical Association, Section of Urology, Banff, Alberta, June 14, 1946.

first visit. Each time bleeding occurred after riding a tractor. There were no other symptoms of any kind.

General physical examination and the usual laboratory procedures revealed nothing abnormal. A cystoscopic examination on June 5, showed a normal bladder. A scout film showed no suspicious shadows or bone lesions. Retrograde pyelograms were interpreted as being normal. The patient was advised to return in six months for further study, but because he had no symptoms he did not return until he had painless hæmaturia again more than two years later.

On November 28, 1942, a cystoscopic examination showed a normal bladder. Scout film showed no suspicious shadows. Retrograde pyelograms (Fig. 2) showed a normal kidney and ureter on the right side. On the left the calices and pelvis were moderately dilated and the ureter dilated to within two inches of the bladder. Congenital obstructive lesions in the lower ureter are usually at the bladder wall. There was no shadow of stone and no history of pain suggestive of kidney origin. In view of painless hæmaturia and an obstructive lesion in the ureter about two inches from the bladder it was thought the lesion might be carcinoma. An exploratory operation was advised but the patient did not return for this until he had another episode of painless hæmaturia nearly four months later.

On March 27, 1943, under spinal anæsthesia the lower left ureter was explored extraperitoneally through a Gibson incision. There was a mass in the ureter near the bladder which was thought to be tumour. Ureterectomy was therefore performed, removing a cuff of bladder wall around the ureteral orifice and as much of the periureteral tissues as possible. The ureter was divided above the pelvic brim and the upper end brought out through a stab wound and drained with a catheter as in cutaneous ureterostomy. The bladder was closed and drained with a urethral catheter. The wound was closed in the usual manner. Convalescence from this operation was uneventful and nephrectomy was performed ten days later, April 6.

Pathological examination of the lower ureter revealed an infiltrating papillary carcinoma surrounding the entire lumen of the ureter about 2 cm. long. It was located approximately 4 cm. from the bladder. Microscopic examination revealed a papillary squamous cell carcinoma, grade 3. There were no tumours in the upper ureter or in any part of the pelvis or calices. Cystoscopic examination November 20, 1943, revealed no evidence of recurrent tumour.

The patient was not seen again until January 3, 1946, when he was passing bloody urine at times and with great frequency, urgency and a small stream. There was a half-ounce residual urine which was cloudy and contained much blood and pus. Rectal examination showed a firm mass in the region of the prostate and base of the bladder which was considered recurrent carcinoma. Cystoscopy January 5, revealed carcinoma infiltrating the prostate, base and anterior wall of the bladder. Tissue was removed with the resectoscope in the hope of enlarging the bladder neck and making urination less difficult. There was spread of infection into the surrounding tissues and the patient died of retroperitoneal cellulitis January 16. Post-mortem examination revealed extensive spread of carcinoma through the prostate, base, and anterior wall of the bladder and into the perivesical tissues. There were metastases in the pelvic lymph nodes. There was suppurative pyelonephritis with multiple abscesses in the kidney. There was retroperitoneal infection in the pelvis with beginning abscess formation.

CASE 3

Mr. J.P.M., aged 80, was referred to our clinic on December 21, 1945, on account of hæmaturia. He had had gross painless hæmaturia many times during the preceding two years. There were no other symptoms referable to the urinary tract. He was in remarkably good health and general physical examination revealed nothing abnormal for a person of his age. Routine laboratory tests were normal.

A cystoscopic examination performed under anæsthesia on December 28, showed a normal bladder and prostatic urethra. A catheter passed easily up the left ureter but on the right side an impassable obstruction was encountered about four inches from the ureteral orifice. Bilateral pyelograms (Fig. 3) showed a normal left kidney with compensatory hypertrophy. On the right were multiple filling defects in the lower ureter and above the pelvic brim enormous dilatation and tortuosity of the ureter. The kidney pelvis was not filled. On

Fig. 1. Case 1.—Showing filling defects in the dilated lower end of a partially filled right ureter. **Fig. 2.** Case 2.—Showing normal right kidney and ureter. There is considerable dilatation of pelvis, calices, and the ureter to a point about two inches from the bladder, below which the lumen of the ureter is completely obliterated. **Fig. 3.** Case 3.—Showing normal left kidney with compensatory hypertrophy. There is a huge dilatation of the right ureter with filling defects in the lower ureter and obliteration of that part adjacent to the bladder.

December 31, the right lower ureter was exposed through a Gibson incision. It was found dilated and near its lower end tumour masses could be palpated through the wall of the ureter. There was no infiltration of the ureteral wall or surrounding tissues. The lower ureter was mobilized and removed with a circular cuff of bladder wall around the ureteral orifice. The opening in the bladder was closed by suture and the bladder drained with a urethral catheter. The ureter was divided above the pelvic brim, the lower tumour-containing segment being removed and the upper end brought out through a stab wound and drained with a catheter as in cutaneous ureterostomy. Convalescence from this operation was uneventful. Nephrectomy was performed January 7, 1946, and again he made a rapid recovery.

Pathological examination showed multiple papillary tumours in the lower ureter. Microscopic examination proved them to be grade 1 papillary squamous cell epithelioma. There were no tumours in the upper ureter or pelvis of the kidney. The kidney was a thin hydronephrotic shell.

The patient was seen last on April 12, 1946, at which time his urine was normal, his incisions solidly healed and his general health good.

PATHOLOGY

There is considerable difference of opinion in regard to the pathological classification of tumours of the ureter. Scott[7] mentions 22 different terms which have been applied to them. Perhaps the most simple and best classification is that presented by Broders wherein the tumours are divided into four grades according to

their relative degrees of malignancy. Ureteral mucosa resembles bladder mucosa. Likewise tumours of the ureter resemble bladder tumours not only in their microscopic appearance but also in their clinical behaviour. They are usually squamous cell epitheliomas and tend to be papillary. Those of lower grades of malignancy tend to be multiple whereas more malignant tumours are usually single. Metastases from these lesions seem to occur more readily than from tumours in the bladder, perhaps because of the thinner wall of the ureter and richer lymphatic system. Metastases usually occur first in the regional retroperitoneal lymph nodes and after that other nodes or almost any organ in the body may be involved. There will be dilatation of the ureter above the tumour and hydronephrotic destruction of the kidney proportional to the degree of ureteral obstruction produced by the tumour.

More than half of all ureteral tumours occur in the lower third of the ureter. The right ureter is involved more frequently than the left. Almost twice as many cases occur in men as women. The average age is approximately 55 years. Cases have been reported from the ages of 22 to 69. Most of the cases occur in the sixth and seventh decades.

SYMPTOMS

The prominent symptoms are hæmaturia and pain. A mass is less frequently encountered. Hæmaturia occurs in 70% of the patients and its character is too variable to be of help in determining its source. Pain occurs in more than 60% of cases. It may be due to ureteral obstruction and vary from a dull ache in the kidney region to typical renal colic. Pain due to local invasion or metastases will depend on the structure involved. A mass is noted in 40% of cases and this is generally the associated hydronephrotic kidney In some cases the ureteral tumour itself has been palpated by abdominal, rectal or vaginal examination. Metastatic lymph node involvement may be found.

Although small fragments of tumour have been discovered in the urine, an examination of the urine is of little value in diagnosis except to show blood cells if the tumour is bleeding at the time of examination and pus cells if secondary infection has occurred. Infection may occur in the obstructed and dilated ureter and kidney altering the clinical picture with superimposed symptoms of renal infection.

DIAGNOSIS

The only pathognomonic sign of ureteral tumour is a constant filling defect demonstrated in the ureterogram. This can be obtained only by retrograde injection of dye through the ureteral catheter. Excretory urograms are of no value in demonstrating filling defects since obstruction produced by the tumour usually results in hydronephrosis and impairs kidney function to a degree that dye is eliminated in faint concentration or more frequently not at all. The plain x-ray or scout film may reveal the outline of an enlarged hydronephrotic kidney on the affected side, coincidental stones or bone metastases.

On the earlier reported cases a preoperative diagnosis was seldom made. In the more recently reported cases a correct diagnosis was made in nearly every instance with information obtained by cystoscopy and retrograde pyelography. A bloody spurt of urine may be seen coming from the ureteral orifice. Associated bladder tumours may be seen. In nearly every case obstruction to the passage of a urethral catheter occurs at the site of the tumour and the tip of the catheter excites profuse bleeding very easily. Occasionally the catheter may pass the tumour and permit the making of a complete pyelogram and ureterogram. More commonly no bougie or catheter will pass beyond the tumour. Usually dye can be injected to outline the involved part of the ureter and show the filling defect with enough dye passing beyond the tumour to show, in part or completely, the dilated ureter and hydronephrosis above. The filling defect should be constant in repeated films to avoid confusion with blood-clot or non-opaque stone. The character of the filling defect varies with the type and location of the tumour. Papillary tumours are likely to be multiple with multiple filling defects and a dilated ureter above the obstructing tumours. A solid infiltrating tumour may have a relatively smooth outline and resemble a stricture with dilatation above.

It is undoubtedly possible to have a tumour too small to be demonstrated. If a kidney is removed because of hæmaturia and inadequate cause for hæmaturia discovered, then the ureter should be removed. If bleeding occurs from the stump of a ureter after nephrectomy then complete ureterectomy must be performed.

TREATMENT

The accepted treatment is complete nephro-ureterectomy with removal of the ureterovesicle segment of the bladder. As much of the periureteral adipose tissue as possible should be removed particularly that portion near the bladder. The operation may be done in one or two stages depending on the skill of the operator. Foord and Ferrier[2] report a mortality rate of 40% in one-stage nephro-ureterectomies and only 5% in two-stage operations. An experienced surgeon with modern anæsthesia and supportive intravenous therapy should have a much lower mortality rate for the one-stage procedure than that reported by Foord and Ferrier. For the average surgeon the two-stage operation should be chosen. The lower tumour-containing segment of the ureter together with a cuff of bladder wall should be removed first and the upper end of the ureter brought out to the skin and drained with a catheter as in cutaneous ureterostomy. Later the kidney may be removed with its attached portion of ureter. Radiotherapy in ureteral tumours can be considered only a palliative procedure.

Because many individuals who have ureteral tumours may and do develop bladder tumours at a later date, every patient should have a routine periodic cystoscopy to discover developing bladder tumours while they are small and can be easily destroyed by cystoscopic fulguration.

PROGNOSIS

Most of the earlier case reports are not accompanied by adequate or, in fact, any follow-up information. The impression which one gains from them is that nearly all patients who survived the operation died of local recurrence or metastases. The report of Counsellor *et al.*[1] contains the most complete follow-up study in the literature. Of the patients with lesions grade 1 or 2, there were seven out of ten alive more than four years following operation. On the other hand only one patient out of eight with lesions grade 3 or 4 was living after two and a half years. The prognosis of ureteral tumours is quite similar to that of bladder tumours. Most of those patients with tumours of relatively low degree of malignancy can be expected to survive whereas most of those with highly malignant tumours will die of local recurrence or metastases.

SUMMARY

1. Three cases of primary carcinoma of the ureter are reported in detail.

2. Hæmaturia is the most common symptom. Pain is second in importance and the finding of a mass is less frequent. The only pathognomonic sign is a filling defect in the ureterogram.

3. The cases illustrate the difficulty usually encountered in discovering the lesion in its early stages. Suspicion of a ureteral tumour should be aroused by the finding of an unexplained hydronephrosis in older patients or hæmaturia in which no other lesion has been found.

4. Prognosis is influenced by the grade of the tumour. Patients with low grade tumours have done well with radical treatment whereas most of those with highly malignant tumours have died in less than three years.

5. The treatment of primary carcinoma of the ureter is complete nephro-ureterectomy with removal of a cuff of bladder wall. For the average surgeon the operation is more safely performed in two stages, with removal of the lower tumour-containing ureteral segment first, followed later by removal of the kidney.

REFERENCES

1. COUNSELLOR, V. S., COOK, E. N. AND SEEFELD, P. H.: *J. Urol.*, **51**: 606, 1944.
2. FOORD, A. G. AND FERRIER, P. A.: *J. Am. M. Ass.*, **112**: 596, 1939.
3. HIGGINS, C. C.: *Ann. Surg.*, **108**: 271, 1938.
4. PILCHER, F. AND MACNAB, D. S.: *Canad. M. A. J.*, **44**: 361, 1941.
5. RAYER, P.: Quoted by Higgins.
6. SCHILLINGS, M. AND SONDERVORST, F. A.: *Rev. belge sc. méd.*, **8**: 225, 1936.
7. SCOTT, W. W.: *J. Urol.*, **50**: 45, 1943.
8. WISING, P. J. AND BLIX, C.: Quoted by Schillings and Sondervorst.

GOWLAND HOPKINS—The early organic chemists worked on natural substances; but their successors, in learning the art of synthesis, entered a new world composed of molecules made by themselves. Frederick Gowland Hopkins, who died on May 16, 1947, re-established biochemistry as a study of life—of vital processes. He urged the organic chemist to "get into touch with the animal", whose body "usually does the unexpected"; and he saw biochemistry as a borderland science, fit meeting-ground for many minds. "It is never", he said, "out of place to urge that the living cell should be thought of as dynamic, and not a static, system", and to this new dynamic biochemistry he made great contributions both by experiment and by quiet leadership. Long ago E. H. Starling spoke truly of his power of "finding among the thickets of ignorance which surround us some path to knowledge which others had passed by unheedingly". His life was one for which we may be grateful.—*The Lancet*, May 24, 1947.

AORTIC ANEURYSMS*

John E. Hill, M.D., C.M.

Vancouver, B.C.

AORTIC aneurysms have for many years been an interesting lesion to clinicians and surgeons. The first were described by Galen in the second century and since that time, many reviews have been published concerning diagnosis and therapy. However, though our knowledge of them has increased immensely, the treatment has been unsatisfactory and, in the main, unsuccessful. With the advent of anticoagulants in vascular surgery and with the refinements of endoaneurysmorrhaphy,[1] combined with wiring and galvanism, it is probable that the operative procedures on these lesions will meet with more and more success. It is for this reason that this pathological review has been undertaken. In addition, a number of the more unusual cases will be presented more fully. No attempt has been made to carry out a full clinical review, as this has been recently and excellently done by Mills and Horton,[2] on many more cases than are here presented.

Aortic aneurysms, in the main, are of two etiological types, atherosclerotic and luetic. Other types have occurred but are extremely rare, such as those following severe injury and mycotic aneurysms arising from infected emboli lodging in the vasa vasorum.

INCIDENCE AND MATERIAL

The incidence of aneurysm varies markedly in different localities, depending on the incidence of syphilis and the adequacy of the antiluetic therapy. The material for this discussion was discovered in 8,044 consecutive autopsies at the Vancouver General Hospital from the years 1936 to 1945, inclusive. In this number there were 82 persons with some type of aortic aneurysm. These autopsies contained approximately twice as many males as females, of all ages, and it is seen that in this locality the incidence of aortic aneurysms is approximately 1%.

Of the 82 aneurysms, 72, or 87.8%, occurred in males and 10, or 12.2% occurred in females. This ratio, when corrected for the preponderance of autopsies on males, is approximately the same as that previously reported by other authors.[2] In 23 cases the aneurysm was a contributory finding and not the primary cause of death.

Age.—Aortic aneurysm is a disease of the older age groups and in this series 93.7% occurred after the age of 50. The youngest patient was 36 and was the victim of an atherosclerotic dissecting aneurysm involving the whole of the aorta. The oldest patient was 84 and his demise was caused by a rupture of an atherosclerotic fusiform aneurysm of the abdominal aorta. However, it would appear that the commonest age group for aortic aneurysm of either luetic or atherosclerotic etiology is from 55 to 75.

Etiology.—In this series, 33 cases, or 40.2%, were of luetic etiology, while 49, or 59.8%, were on an atherosclerotic basis.

Types.—Aortic aneurysms can be classed in anatomical types; *i.e.*, fusiform, saccular or dissecting. In addition, they may be multiple and consist of any combination of those types. It has been previously pointed out that a dissecting aneurysm is an extremely uncommon occurrence with a luetic aortitis, because of the extensive fibrosis which takes place in the adventitia and media.[3] This phenomenon was again seen in this series as we discovered no dissecting aneurysms occurring in a luetic aortitis.

A true dissecting aneurysm is one in which the dissection takes place between the middle and outer thirds of the media.[4] In some of our cases the dissection was evident but the eventual laceration had been so severe that it was impossible to tell whether the tracking was wholly within the layers of the media and, indeed in some sections, it appeared to be tracking between the adventitia and media. However, all cases where a definite dissection between any coats of the aorta could be found were classed as dissecting aneurysms.

In this series, 42.7% had a single saccular aneurysm, 24.4% a single fusiform aneurysm, 20.7% dissecting aneurysm and 12.2% showed multiple aneurysms. The incidence of multiple aneurysms is slightly greater than previously reported.

Position.—The position of the aneurysm in the aorta is important, both for diagnosis and therapy. To denote position in this discussion,

* From the Department of Pathology, Vancouver General Hospital, Vancouver, B.C.

Presented to the Staff Clinical Meeting of the Vancouver General Hospital, February 25, 1947.

the aorta was divided into five anatomical areas, as follows:

Area 1.—Between the aortic cusps and the innominate artery.

Area 2.—Between the innominate artery and the left subclavian artery.

Area 3.—Between the left subclavian artery and the cœliac axis.

Area 4.—Between the cœliac axis and the inferior mesenteric artery.

Area 5.—Between the inferior mesenteric artery and the bifurcation of the aorta.

It can be readily seen that many of the aneurysms will be placed in more than one area, particularly those of the dissecting variety, some of which extended throughout the whole length of the aorta (Fig. 1).

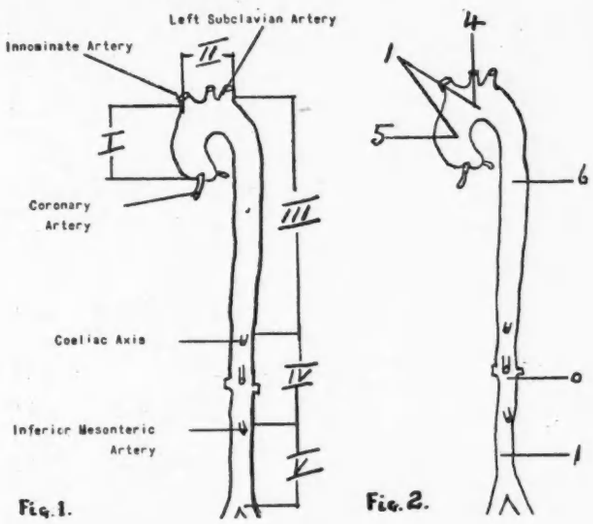


Fig. 1.—Areas. **Fig. 2.**—Distribution of 17 luetic saccular aneurysms.

Of the 35 cases of single saccular aneurysms, 17 were of luetic origin and 18 of atherosclerotic origin. In the 17 of luetic origin, 5 were in Area 1, 4 in Area 2, 6 in Area 3, 1 in Area 5, and 1 case involved more than one region; *i.e.*, Area 1 and Area 2. Thus, saccular luetic aneurysms are nearly completely confined to the arch and descending thoracic portions of the aorta, with a slight predilection for the ascending aorta and thoracic descending aorta over the actual arch. There is only one case of a single saccular luetic aneurysm occurring in the abdominal aorta (Fig. 2).

Now, in considering the saccular aneurysms of atherosclerotic origin, we find that of the 18 cases, 5 were in Area 1, 1 in Area 2, 2 in Area 3, 4 in Area 4, and 4 in Area 5. Two involved more than one area, 1 in Areas 1 and 2, and 1 in Areas 4 and 5. From this, it is seen that atherosclerotic aneurysms are commonest at both ends of the aorta and tend to be more common in the abdominal aorta than in the thoracic. This is as would be expected, as the earliest appearing atherosclerosis is usually seen in the ascending aorta and towards the bifurcation of the aorta (Fig. 3).

When the single fusiform aneurysms were reviewed, it was found that of the twenty cases, 10 were of luetic etiology and 10 of atherosclerotic etiology. In those of luetic etiology, 5 occurred in Area 1, 1 in Area 3, and 4 cases involved more than one Area, 3 involving Areas 1 and 2, and one involving Areas 2 and 3. In the fusiform atherosclerotic aneurysms, one occurred in Area 1, one in Area 2, one in Area 3, one in Area 4, three in Area 5 and three showed involvement of more than one Area, two involving Areas 1 and 2, and one involving Areas 4 and 5. Thus the fusiform aneurysms have the same distribution as the saccular aneurysms, the luetic ones occurring mainly in the ascending arch, and to a lesser extent the descending thoracic aorta, while the atherosclerotic ones tend to occur at both ends of the aorta. The fusiform aneurysms show a greater tendency to involvement of more than one segment of the aorta than do the saccular (Figs. 4 and 5).

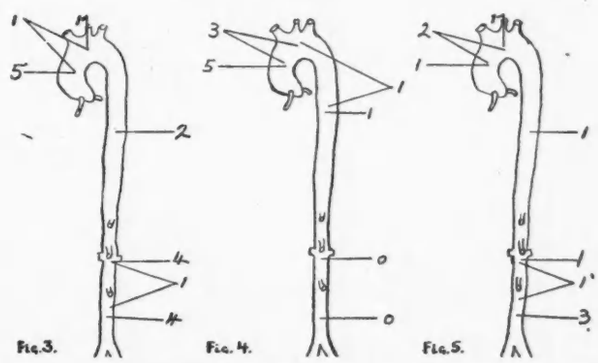


Fig. 3.—Distribution of 18 cases of atherosclerotic saccular aneurysms. **Fig. 4.**—Distribution of 10 luetic fusiform aneurysms. **Fig. 5.**—Distribution of 10 atherosclerotic fusiform aneurysms.

In reviewing the dissecting aneurysms; as stated previously, they were all of atherosclerotic etiology. They were, as would be expected, found frequently involving more than one segment of the aorta, 3 where wholly situated in Area 1, one in Area 2 and two in Area 3. In the remaining dissecting aneurysms, 9 began their dissection in Area 1 and extended for a variable distance, some as far as the

bifurcation; one originated in Area 2 and one in Area 4. Thus, it may be concluded that a dissecting aneurysm nearly always originates in the ascending, arch, or upper portion of the descending thoracic aorta. However, it may extend for a variable length, even to involving the whole of the aorta. The length of extension depends entirely on where it ruptures, either externally or back into the aortic lumen.

Multiple aneurysms were seen to be of luetic etiology in 6 cases and of atherosclerotic etiology in 4 cases. Of the luetic cases, they occurred as saccular or fusiform dilatations, or combinations of these with no particular rhyme or reason. All but two occurred above the diaphragm. In one case there were seen five separate saccular aneurysms, one occurring in Area 2, three in Area 3, and one in Area 4. These aneurysms, particularly those of the saccular variety, tended to be smaller than the single large ones usually seen, and appeared as golfball-sized out-pouchings of the aorta.

In the multiple aneurysms of atherosclerotic etiology, the majority appeared in Areas 4 and 5; *i.e.*, below the diaphragm. One case showed a fusiform aneurysm in the ascending aorta and two saccular aneurysms near the bifurcation. Two of the cases showed a dissecting type of aneurysm along with the other, either fusiform or saccular varieties. In these cases the dissecting type of aneurysm originated in Areas 3 and 4, respectively.

Involvement of Great Vessels

It would appear that in any therapeutic attack on aneurysms the relation of the ostia of great vessels would be of importance, as the patency of these must be maintained. For this reason, an attempt was made to determine the number of times great vessels were found originating from the sac. This portion of the review was confined to those aneurysms of the fusiform or saccular variety. Including those cases of multiple aneurysms, 62 fusiform or saccular lesions were identified. Of these, 38 had no great vessel originating from the sac wall and 24 had a vessel originating from the sac. In the case of those aneurysms in Area 1, the coronary arteries were the vessels of concern. In general, the usual aneurysms in this area began above the coronary ostia. However, in several of the luetic lesions, intimal proliferation had occluded the openings. As would be expected, Area 2 showed the highest rate of involvement, nearly all aneurysms having a vessel originating from the sac. Only the occasional sac was found on the inferior surface of the arch. Areas 3 and 5 were singularly free of vessel involvement with only the occasional Area 5 aneurysm showing one or both of the common iliac arteries originating from the sac. Area 4 showed the next highest great vessel involvement to Area 2. In this case, the usual vessels involved were the renal arteries, the inferior mesenteric artery or the superior mesenteric artery. The cœliac axis was singularly free of involvement in lesions of this area.

Lamination and Clotting

Nature's reparative attempts in aneurysmal lesions consist of a laying down of tough, organized, laminated thrombus along the lining of the sac. It would appear that both the ability of the human to form this thrombus, and the quality of the thrombus formed, have much to do with the life expectancy of that individual. As thrombus is laid down and the lumen of the vessel decreased, it is seen from the laws governing the flow of liquids in tubes, that the lateral pressure on that portion of the aorta will likewise be decreased. This statement is derived from the following laws. (1) Lateral pressure is inversely proportional to the velocity; (2) pressure head remaining constant then the velocity is directly proportional to the sectional area of the tube (part of Poiseuille Law).

In nearly all cases which were autopsied because of a rupture of a fusiform or saccular aneurysm, either one found an aneurysm in which there was no thrombus, or an aneurysm in which there was laminated thrombus which in one area showed a softening with resultant break-through of the clot and underlying aortic wall. It is probable that any therapeutic attempt on aneurysms will probably depend on the ability of the procedure to lay down clot in the sac or increase the toughness of the clot laid down. It is for this reason that the organization of the clot in the aneurysm sac was studied. To facilitate the classification of thrombus formation, the clot was classed as minimal, with only a few shreds of thrombus attached to the sac; moderate, with a definite layer of firm clot; or marked, with a nearly complete filling of the sac by firm, well organized laminated thrombus.

It was possible to review 78 of the aneurysms of both saccular and fusiform varieties in this respect. There were 48 saccular aneurysms, of which 15 showed marked, 21 moderate and 12 minimal thrombus formation. There were 30 fusiform aneurysm, of which 2 showed marked, 3 moderate and 25 minimal thrombus formation. From these figures, it is seen that approximately 75% of saccular aneurysms have good thrombus formation and therapy should be directed at strengthening this thrombus; whereas 83% of fusiform aneurysms show poor clot formation and therapy should be directed at laying down new thrombus. With the refinement of technique of arteriography, it will be possible to study the thrombus formation in aneurysms and possibly introduce the required therapy.

BONY EROSION

Evidence of erosion of adjacent bony structures by aneurysms was looked for in all cases of fusiform or saccular aneurysms. Six cases of bony erosion were found. As has been previously reported, the luetic aneurysm is the main offender in this aspect. In five cases, the aneurysms were of luetic origin. Four occurred in Area 3 and eroded underlying vertebræ, while one occurred in Area 2 and eroded sternum, ribs and clavicles. One of these cases showed a fusiform aneurysm, while the other four showed saccular aneurysms.

The case of an atherosclerotic aneurysm eroding the vertebræ is very interesting and will be reported more fully below. It was a saccular aneurysm of Area 2 which protruded medially, to erode the adjacent vertebræ. Microscopic sections through the vertebræ, however, showed the picture of a plasma cell myeloma. It would appear that atherosclerotic aneurysms, for some reason, will not erode normal bony structures.

SITE OF RUPTURE

In all cases of ruptured aneurysms, fusiform, saccular or dissecting, the site of rupture was studied to determine if any particular portion of the aortic trunk were more liable to rupture than any other portion, and also to help determine what bizarre symptom complexes may be expected following rupture. Atogether, there were 50 aneurysms of all types which ruptured and the tissues into which they ruptured are as follows:

DISSECTING ANEURYSMS—11 CASES

10 ruptured into pericardium.
1 ruptured into post mediastinum

SACCULAR AND FUSIFORM ANEURYSMS

In area 1—6 cases.
1 ruptured into right pleural cavity.
1 ruptured into right lung parenchyma.
3 ruptured into pericardium.
1 ruptured into superior mediastinum.

In area 2—5 cases.
2 ruptured into posterior mediastinum.
1 ruptured into left pleural cavity.
1 ruptured into trachea.
1 ruptured into pericardium.

In area 3—11 cases.
5 ruptured into left pleural cavity.
2 ruptured into posterior mediastinum.
1 ruptured into right main bronchus.
2 ruptured into left upper lobe bronchus.
1 ruptured into œsophagus.

In area 4—5 cases.
5 ruptured into retroperitoneal tissues.

In area 5—7 cases.
5 ruptured into retroperitoneal tissues.
1 ruptured into inferior vena cava.
1 ruptured into peritoneal cavity.

SACCULAR AND FUSIFORM ANEURYSMS INVOLVING MULTIPLE AREAS—5 CASES.

2 in areas 4 and 5—ruptured into retroperitoneal tissues
1 in areas 3 and 4—ruptured into posterior mediastinum.
1 in areas 2 and 3—ruptured into left pleural cavity.
1 in areas 1, 2 and 3—ruptured into left lung parenchyma.

From the above figures it may be concluded that the tendency of an aortic aneurysm to rupture is no more frequent in one site than another. However, it may be mentioned that it is my personal observation that the actual site of rupture is more likely to be at the point where a great vessel joins the aorta; *e.g.*, junction of a renal vessel to aorta. It can also be seen that a ruptured aneurysm is not necessarily a cause for sudden death, because of the formation of a false sac. The author recently has seen a case of an atherosclerotic aneurysm of the abdominal aorta in Area 4 which ruptured into the retroperitoneal tissues and the patient remained alive for several days. During this time she began to develop a hæmaturia which suddenly increased in its severity and the patient died. In this case, at autopsy the ruptured aortic aneurysm was found; then an area of false sac and, further, lateralward, a rupture of the false sac into the left renal pelvis.

A few of the more unusual aneurysms will be recorded below:

CASE 1

A 47-year old white male logger, of Swedish extraction, was admitted to hospital July 21, 1939, complaining of swelling on front of neck—4 months; dysphagia—2 weeks; cough—2 weeks; and hoarseness—1 week. Twenty years before admission he had had an urethral discharge but no history of treatment could be elicited. The physical examination revealed a midline episternal swelling, approximately 11 x 9 x 13 cm., between the

sternal notch and thyroid cartilage. Skin over this area was tense and red but the colour faded on pressure. The mass pulsated with each heart beat with an expansile thrust in all directions. The examining fingers could be pushed into the mass and pulsations were felt to be increased. The remainder of the physical examination was negative. On August 1, 1939, the right arm showed a lymphœdema above the middle of the forearm. Blood pressures recorded in both arms at this time showed right 114/82 and left 125/80. On August 10, 1939, the patient died of what appeared to be asphyxia.

At autopsy, a large saccular aneurysm arising from the uppermost portion of the aortic arch was discovered. The left common carotid artery and the left subclavian artery originated from the sac. The sac itself had a moderate thrombus formation. Both clavicles were eroded, the ends projecting into the sac. All ribs down to the 6th, on the left and 5th on the right projected into the sac. At this level there was no sternum found and in the clot itself were discerned a number of small bits of cancellous bone. The trachea had been nearly completely compressed in the superior mediastinum. The remainder of the aorta showed in a number of areas in the ascending and thoracic portion, the typical longitudinal puckering of luetic aortitis. The Kahn test was positive. Diagnosis: Massive saccular aneurysm of the arch of the aorta eroding sternum, left upper five and right upper four ribs, clavicles and compressing the trachea.

CASE 2

A 41-year old white male came to autopsy on October 18, 1939. No history was available as this was a case of sudden death. At autopsy the heart was hypertrophied and dilated, weighing 780 gm. A valved but patent foramen ovale was discovered; the aortic valve consisted of two cusps only. At the uppermost part of the ascending aorta was a split in the intima and a typical dissecting aneurysm was present tracking down the ascending aorta to rupture into the pericardial sac. Just distal to the innominate artery the aorta was coarcted for a distance of 1.5 cm. Just distal to the coarctation was a persistent ductus arteriosus and distal to this the left common carotid and left subclavian artery were seen arising from the aorta. A marked degree of atherosclerosis was present in the aorta proximal to the coarctation while virtually none was present in the distal portion. The right internal mammary artery was over twice the size of the left internal mammary and showed definite atherosclerosis. Diagnosis: Hæmopericardium, dissecting aneurysm of the ascending aorta, coarctation of the aorta, patent ductus arteriosus.

CASE 3

A 68-year old white male was admitted to hospital on May 17, 1941, complaining of distended abdomen, cough and mid-back pain. All symptoms had been present for eight weeks. There was a past history of syphilis and gonorrhœa contracted 40 years previously. The syphilis had received some treatment. Physical examination showed distended, and in some cases thrombosed, superficial veins present over the left anterior wall extending up into the left axilla and suprasternal notch. An aortic systolic and diastolic murmur was present and a pitting œdema of both lower legs. Blood pressure was 160/70 in both arms. An electrocardiogram showed a bundle branch block. X-ray of the heart, great vessels and spine showed a left-sided widening of the aortic arch and a concavity of the anterior surface of the ninth thoracic vertebra.

At autopsy, on May 26, 1941, a saccular aneurysm of Area 2, measuring 6 x 4 x 2 cm. and eroding the left antero-lateral portions of the third and fourth thoracic vertebræ, was found. In the aneurysm was a moderate quantity of laminated thrombus. In addition, a number of white cellular lymph nodes and similar white cellular plaques present on the mesentery, were discovered. On microscopic examination the aneurysm was of atherosclerotic etiology and the underlying vertebræ, the lymph nodes and the mesenteric plaques showed typical plasma cell myeloma. No evidence of any luetic process was discovered.

CASE 4

A 50-year old white male was admitted to hospital on April 4, 1943, with the complaints of "influenza feeling" and a severe, hacking, non-productive cough—6 weeks; weakness—3 weeks; pains in the legs—2 weeks. He had lost seventeen pounds of weight since his onset of symptoms. Physical examination revealed a sick-looking but fairly well nourished man. Temperature was of a spiking variety with a high in the evening up to 103° F. Pulse 100; respirations 20. There was pitting œdema of both ankles and feet. Cardiac examination revealed a loud blowing systolic mitral murmur and a systolic aortic murmur. The white blood count during his hospital stay was consistently elevated in the region of 18,000 c.mm. His red blood count showed a severe hypochromic anæmia down to 2,500,000 c.mm. Repeated blood cultures were consistently negative. Kahn was negative and repeated urinalysis showed a plus 3 albuminuria and a variety of casts, red and white blood cells and sediment. Electrocardiogram showed a sinus tachycardia and x-ray of the thorax revealed nothing of note. The treatment consisted of repeated blood transfusions. On April 26, 1943 he became markedly dyspnœic and began to cough up frothy bloody sputum and on April 28, 1943, he expired.

At autopsy the lungs were markedly congested. The mitral and aortic valve showed some fibrous thickening along the bases of the cusps. In the ascending aorta just above the left coronary ostium was an atherosclerotic aneurysm 3 cm. in diameter. Lining the sac was a moderate layer of laminated thrombus and over this and attached to the edges of the aneurysm was a soft, friable, typical bacterial vegetation. Cultures of this were spoiled but there was no doubt that this vegatation was infected. Infarcts were found in the spleen and left kidney.

CASE 5

A 70-year old white male was admitted to hospital January 11, 1944, complaining of gangrene of right small toe. Four weeks previously he had a severe cramp in the right calf muscles which was followed by swelling of the right foot and ankle and sloughing of the skin between the toes. On physical examination all the toes of the right foot were swollen and tender to touch. There was a blackened area along the outside of the small toe and extending for a short distance along the lateral surface of the foot. In addition there was a small black area on the tip of the great toe. Dorsalis pedis and posterior tibial pulsations were equivocal. Dermotherm reading showed a very slight response following lumbar sympathetic injection with novocaine anæsthesia. While waiting in hospital for a definite line of demarcation to form before doing definitive surgery, this man was seized with a sudden abdominal pain which proved to be a perforation of an anterior duodenal ulcer. This latter condition caused his demise on February 9, 1944.

At autopsy, a subphrenic abscess and the perforated duodenal ulcer were found. In addition, there was found, involving Areas 4 and 5, a 14 cm. in diameter atherosclerotic saccular aneurysm. The iliac vessels originated from the inferior edge of this aneurysm. The sac was nearly completely filled with well laminated thrombus and this thrombus completely occluded the right common iliac artery and partially occluded the left common iliac artery. The right leg from the ankle to the groin was reddened, swollen and œdematous. The small toe had sloughed off.

CASE 6

This was a case of sudden death and no history was available. The patient was a 62-year old white male who expired suddenly on September 14, 1944. Both lungs were found to be markedly congested and œdematous while in the pulmonary artery were found a number

of large chunks of well organized thrombus, obviously of ante-mortem quality. These were completely blocking the artery and the patient had obviously died of a massive pulmonary infarction. A typical luetic aortitis was found in the aorta while in Area 5 there was present a 20 cm. in diameter saccular aneurysm which was lined by irregular quantities of laminated thrombus. At the posterior margin of this aneurysm the sac was adherent to the inferior vena cava and an arterio-venous fistula was present between these two structures. Through this perforation, bits of thrombus lining the aneurysm had passed to form the massive pulmonary emboli previously mentioned.

SUMMARY

1. Eighty-two cases of aortic aneurysms which have come to autopsy have been reviewed as to incidence, age, sex, etiology, anatomical type and position.

2. An attempt has been made to study great vessel involvement, bony erosion and laminations.

3. A study has been made to ascertain at which sites an aneurysm is most likely to rupture.

4. A suggestion has been made as to the form any therapeutic attack should take on saccular and fusiform aneurysms. This therapy would be in addition to the treatment of the underlying cause.

5. Six cases of unusual aneurysms have been presented more fully.

The author expresses his appreciation to Dr. H. H. Pitts, Director of Laboratories, Vancouver General Hospital, for his assistance in preparing this paper.

REFERENCES

1. BLAKEMORE, A. H.: Nelson Looseleaf Surgery, 1: XII B, 785.
2. MILLS, J. H. AND HORTON, B. T.: *Arch. Int. Med.*, 62: 949, 1938.
3. SHAPIRO, L.: *Canad. M. A. J.*, 49: 408, 1943.
4. BOYD, W.: Textbook of Pathology, 4th ed., 401, 1943.

THE EFFECT OF ATABRINE ON AURICULAR FIBRILLATION IN MAN*

Menard M. Gertler, M.D. and Stephen B. Yohalem, M.D.

New York, N.Y.

AURICULAR fibrillation is a serious cardiac abnormality which probably results from the onset of one or more circus movements in the atrial musculature.[1] Fortunately, this malady may ofttimes be controlled by the judicious use of quinidine or digitalis.[1]

The beneficent effects of quinidine in auricular fibrillation were shown by the late Sir Thomas Lewis and his coworkers[2] to be dependent on several factors, namely: (*a*) lengthening of the refractory period in atrial musculature by direct action and by decreasing vagal inhibitory influence on the atrium; (*b*) decreasing the rate of conduction in atrial muscle; (*c*) depressing A-V conduction. Furthermore Lewis[3] suggested that quinidine was five to ten times more effective than its isomer, quinine, in this action.

Evidence has accumulated in the literature concerning the unusual parallelism of physiologic properties between atabrine [3 chloro-7 methoxy-9 (1 methoxy-4 diethylaminobutylamine) acridine] and quinine (quinoline linked with quinucleotide by means of an alcohol). In spite of their totally different chemical structures, they both inhibit choline esterase extracted from the electric organ of *electophorus electricus;*[4] dilate the coronary arteries of the perfused rabbit's heart;[5] inhibit the gastric secretion produced by rhythmic vagal stimulation;[6] increase the refractory period and decrease the excitability of the motor end plate in striated and smooth muscle;[7, 8, 9] depress excitability in the perfused rabbit and frog heart.[7, 8, 10]

Shortly after Babkin and Ritchie[11] demonstrated that quinine partially paralyzed the vagal inhibitory fibres to the dog heart, it was observed by Gertler and Karp[12] that atabrine produced the same effects. In addition the action of atabrine like quinine was antagonized by eserine and antagonistic to mecholyl. This parallelism and the established efficacy of quinidine, an isomer of quinine, in restoring regular sinus rhythm to hearts in auricular fibrillation and supraventricular tachycardia, suggested that atabrine would be similarly effective. Experiments devised by Gertler and Karp[13] to test the validity of this concept bore out all expectations. Atabrine, injected intravenously restored almost immediately regular sinus rhythm in animals with experimentally produced auricular fibrillation and supraventricular (nodal) tachycardia of the vagal type.[14] It is of interest to report that Ganguli[15] in his study of the effect of atabrine on the electrocardiogram includes one case of auricular fibrillation in a patient being treated for malaria with atabrine. The rhythm reverted to normal sinus rhythm. It cannot be stated with certainty whether this was due directly to the action of atabrine on the myocardium or to other drugs since Ganguli does not refer specifically to this case.

* From the Second Medical Service and the Cardiology Department of the Mount Sinai Hospital, New York, N.Y.

Those familiar with the use of atabrine in the treatment of malaria regard the drug as virtually nontoxic in therapeutic dosage. Furthermore, as far as could be ascertained from the experimental[5, 12, 13] and clinical[15, 16] evidence, atabrine in therapeutic doses is nontoxic to the myocardium. The sole exception to this is found in the work of Smith and Stoeckle[17] who injected massive doses of atabrine into the heart lung preparation of dogs. Their interpretations can be questioned by reason that atabrine at such concentrations is strongly acid and that the sudden infusion of strong acid solutions may produce similar if not identical effects.[18]

Thus with experimental evidence in animals as a preliminary and with assurance that atabrine in therapeutic dosage is nontoxic to the myocardium, this study of the effectiveness of atabrine in restoring normal sinus rhythm in auricular fibrillation was undertaken.

CASE 1

W.B. This 55-year old white salesman was admitted to the hospital in July, 1946. He had been well until the morning of admission when he awoke with a tender burning red area over the left malleolus, an area which rapidly spread to involve the whole leg. Fifteen and twenty years prior to admission similar lesions in the same area had been present. For three days prior to admission he had had frequent loose non-bloody stools without cramps. He felt both chilly and feverish.

Physical examination revealed an acutely ill male appearing older than his stated age. The temperature was 104.6 with a pulse of 80. No abnormalities were noted except for a brawny red tender swelling of the left leg without cords.

The patient was treated for erysipelas of the leg with penicillin and sulfadiazine. The local lesion subsided in three days but fever, bradycardia, and diarrhœa remained. Repeated cultures of blood, stool, and urine revealed no pathogens and agglutinations against all the enteric organisms were persistently negative. On the ninth hospital day, auricular fibrillation suddenly developed. Previous electrocardiograms had not been abnormal; 0.6 gm. of atabrine in 10 c.c. 1% novocaine was administered intramuscularly with return of normal sinus rhythm in two and one-half hours. On the twelfth hospital day a second onset of auricular fibrillation was observed.

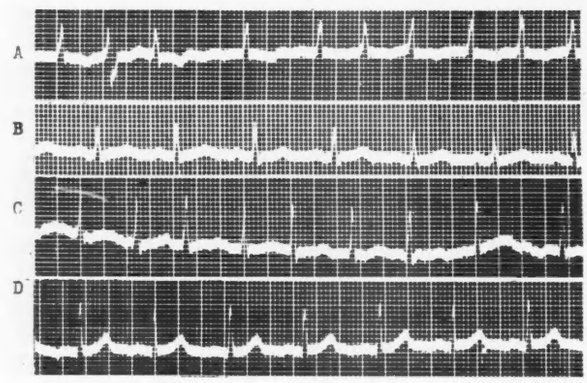


Fig. 1.—W.B. (A) Auricular fibrillation, ventricular rate 83 to 150. (B) Regular sinus rhythm 2½ hours following an intramuscular injection of 0.6 gm. atabrine, rate 83. (C) Three days following (B), auricular fibrillation, ventricular rate 80 to 145. (D) Regular sinus rhythm 2 hours after the second injection of 0.6 gm. atabrine intramuscularly, rate 90. All records shown are standard lead 2.

The initial dose was repeated at twelve hour intervals and two hours after the second injection the rhythm became regular (Fig. 1); 0.1 gm. orally was given thrice daily for three days and then daily for three more. By this time the patient's temperature had fallen to normal and his diarrhœa had stopped. Convalescence was uneventful and he was discharged, the diagnostic impression being erysipelas and of enteric fever of unknown type with myocarditis.

CASE 2

C.P. This 48-year old Negro bartender was admitted in August, 1946. He had been well until the month prior to admission when he first noted dyspnœa and palpitation on climbing two flights of stairs. Three days prior to admission his legs began to swell and severe orthopnœa with paroxysms of nocturnal dyspnœa supervened. At the age of fifteen he had had a penile sore which healed in three weeks without therapy.

The patient was acutely ill. The heart was enlarged to the left and downward. There was a long loud diastolic murmur at the aortic area transmitted to the apex, and palpable diastolic basal thrill. Capillary pulsation and the sign of Duroziez were present. The tender liver was palpable four fingers below the costal margin. Pretibial and ankle œdema were moderate. Blood pressure 145/55.

Treatment was begun with oxygen, a mercurial diuretic, strophanthin (Burroughs-Wellcome) 0.3 mgm. by vein, and digitalis leaf. Following rapid clinical improvement he was maintained on 0.1 gm. digitalis leaf daily. Blood Kahn and Wassermann were positive. The electrocardiogram showed left ventricular involvement and strain with progressive widening of the P-R interval to 0.32 sec. On the third hospital day auricular fibrillation began.

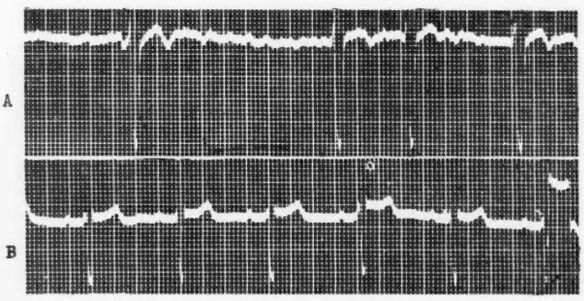


Fig. 2.—C.P. (A) Auricular fibrillation, ventricular rate 33 to 90. (B) Regular sinus rhythm (rate 75) 2 hours following the second injection of 0.4 gm. atabrine intramuscularly. Records shown are CR2.

The patient had had 1.6 gm. digitalis leaf and 0.3 mgm. strophanthin in two days; 0.4 gm. atabrine was administered intramuscularly without effect. It was repeated in twelve hours, and two hours later normal sinus rhythm was present; 0.1 gm. orally was continued daily for three days with no further abnormalities of rhythm. The patient made a good recovery. The final impression was luetic heart disease with aortic insufficiency, enlarged heart and congestive failure (Fig. 2).

CASE 3

F.H. This 49-year old Negro housewife was admitted in July, 1946. Twenty years prior to admission she had had acute rheumatic fever with polyarthritis. She then remained well for eighteen years when migratory polyarthritis again developed and a diagnosis of rheumatic myocarditis was made. Subsequently she remained

chronically ill. Three weeks prior to admission, the right knee became tender and swollen. This subsided but the patient was awakened at night gasping for breath and extremely apprehensnve. She then came to the hospital.

The patient was acutely ill with marked cyanosis and dyspnœa. Fine crepitations were audible over the whole chest. The heart was enlarged to the left and right. Harsh apical systolic and diastolic murmurs were associated with a double thrill. A separate aortic blow was present. The blunt, slightly tender liver was palpable five fingers below the costal margin. Neck veins were distended with a hepatojugular reflux. Blood pressure 150/70.

The patient was treated with positive pressure oxygen, digitalin nativelle, mercuhydrin, morphine, and bloodless phlebotomy with rotating tourniquets. Salicylates were administered for the acute rheumatic fever. She improved rapidly but was never completely free of signs of failure. On the thirteenth hospital day the pulse which had always been regular changed to one of gross irregularity. Electrocardiogram confirmed the diagnosis of auricular fibrillation.

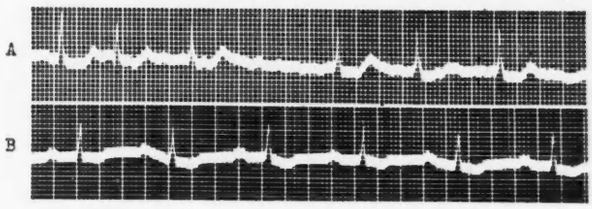


Fig. 3.—F.H. (A) Auricular fibrillation 30 to 110. (B) Regular sinus rhythm (rate 72) 2½ hours following the injection (I.M.) of 0.4 gm. atabrine. Records shown are from standard lead 2.

Apprehension was marked; 0.4 gm. of atabrine was given intramuscularly with restitution of a regular rhythm in two and one-half hours. The patient felt much improved. Subsequently the rhythm remained regular and the patient slowly recovered. The final impression was active rheumatic fever with myocarditis, mitral stenosis and insufficiency, and congestive failure.

CASE 4

M.F. This 79-year old white male was admitted for the second time in November, 1946. He had been hospitalized previously in October, 1945, for a bleeding duodenal ulcer. Ten days prior to admission he had developed pernicious vomiting and tarry stools with progressive weakness.

He was dehydrated, malnourished, and critically ill. The heart rate was normal; the sounds were of poor quality. Blood pressure 130/65. Stool examination revealed large amounts of occult blood. The hæmoglobin was 37% or 7.5 gm. Initial electrocardiogram showed inversion of T waves in CF1, CF2, CF4 with depression of S-T segments in limb leads 2 and 3.

The patient was treated with blood transfusions, gastric drainage, and small feedings. His course was one of repeated crises with gastric dilatation, hæmorrhage, and shock. On the thirteenth hospital day he began to suffer from auricular fibrillation; 0.3 gm. atabrine intramuscularly was followed by restoration of normal rhythm in four hours. Subsequently 1.2 mgm. digitalin nativelle by vein was given and maintenence was continued with digifolin intramuscularly. At the time of this report the patient is still in critical condition. The heart rate is regular. The impression is of anæmic and arteriosclerotic heart disease with coronary insufficiency and myocardial damage.

CASE 5

M.O. This 58-year old Austrian-born white housewife was apparently well until eight months prior to admission when she noted the gradual onset of shortness of breath, palpitation, and intermittent swelling of the legs. She began to use extra pillows for greater respiratory ease. Digitalis was taken irregularly. About one month after the onset, progressive swelling of the base of the neck became sufficient to cause comment among the patient's relatives. In the eight months of illness, she lost fifty pounds.

The thyroid was much enlarged, firm, and somewhat nodular. There was no bruit. The neck veins were distended. Moist râles were present in both lower lobes. The heart was slightly enlarged to 1 cm. beyond the midclavicular line. A loud apical systolic murmur was present. Auricular fibrillation with marked pulse deficit was apparent. Both liver and spleen were palpably enlarged.

The patient was treated with oral digitalin nativelle and with intramuscular mercuhydrin. Basal metabolic rate after subsidence of the obvious failure was plus 33% and plus 30%. Atabrine 0.4 gm. was administered intramuscularly twice at twelve hour intervals without effect. After preparation with iodine, a subtotal thyroidectomy was performed. One week after operation the auricular fibrillation reverted to normal sinus rhythm. The final impression was thyrotoxic and arteriosclerotic heart disease with enlarged heart, congestive failure, and auricular fibrillation.

CASE 6

S.R. This 58-year old white male was first admitted to the Mount Sinai Hospital in 1933 with signs and symptoms of hyperthyroidism and with auricular fibrillation. The patient was given quinidine 0.4 gm. q.4h. for 6 doses without relief. Thyroidectomy was performed with symptomatic relief but with no effect on the arrhythmia which has persisted until the present time. Subsequently a cholecystostomy was performed on a gangrenous gallbladder. The sinus healed. This admission depended on a recurrence of epigastric and right-sided pain with chills and fever.

The physical findings were compatible with a recurrent cholecystitis. On the fifth day the old sinus ruptured with relief of pain and fever. It healed without incident. While in the hospital, atabrine 0.4 gm. intramuscularly was given twice followed by 0.1 gm. orally thrice daily for three days. The heart rhythm was not affected.

CASE 7

M.L. This 31 year old white housewife was first admitted in 1938 at which time she suffered from acute rheumatic fever with mitral insufficiency and stenosis as a sequel. Following this single episode she remained well until January, 1946, when the first signs of decompensation appeared. There was never peripheral œdema. In March, 1946, she began to take digitalis. Cough became an increasingly annoying symptom and, because of this she was ultimately hospitalized.

When examined, the patient did not appear severely ill. The heart was markedly enlarged with a forceful impulse. Diastolic and systolic murmurs were audible at the apex, the aortic and Erb's areas. Those at the base appeared to be separate murmurs. The liver was palpable two fingers below the costal margin. The spleen was not felt. Blood pressure 140/70.

The patient was continued on digitalis. Because of a rapid erythrocyte sedimentation rate, salicylates were administered. The patient's condition became progressively worse with increase in the size of the liver. Gallop rhythm was intermittently present. The P-R interval became longer and measured 0.32 seconds on the fourteenth hospital day. On the following day auricular fibrillation was found. No response was obtained to two injections of 0.4 gm. atabrine intramuscularly; but after the second injection, the patient was nauseated and had a marked diaphoresis. Four days later she began to have abdominal pain and bloody diarrhœa. The impression was of mesenteric embolus. Despite supportive therapy she died. Post mortem examination revealed active rheumatic carditis, insufficiency and stenosis of the mitral, aortic, and tri-

cuspid valves, and mesenteric embolus with gangrene of the small bowel and ascending colon.

CASE 8

E.G. This 59 year old housewife had been well for thirty years following a thyroidectomy for hyperthyroidism. In the early part of 1944, progressive dyspnœa, orthopnœa, and, later, ankle œdema were noted. The dyspnœa suddenly increased at the time of her admission. She had noted palpitation for about eighteen months.

Physical examination revealed a markedly dyspnœic, orthopnœic, cyanotic female appearing older than her stated age. The neck veins were distended. Signs of fluid were present in the right chest to the tip of the scapula, and fine crepitations were audible on the left side and above the fluid on the right. The heart did not appear enlarged. There was a very harsh systolic murmur at the base transmitted to the neck and a systolic thrill over the same area. No diastolic murmur was heard. Auricular fibrillation was present. The smooth liver was palpable three fingers below the costal margin.

The patient was treated with diuretics and digitalis with but a poor response. Fluid mechanically removed from the chest reaccumulated rapidly. Calcification of the aortic valve was demonstrated fluoroscopically. No enlargement of the auricle could be demonstrated. Atabrine 0.6 gm. intramuscularly was twice exhibited with no effect on the arrhythmia. Basal metabolic rate was reported as plus 48%. On treatment with iodides, there was some improvement which had not been maintained with propylthiouracil at the time of this report. Quinidine in 0.4 gm. oral dosage at two hour intervals for 6 doses was also ineffective in altering the heart rate. At the time of writing this report the patient was still in congestive failure. The impression was thyrotoxic and (?) rheumatic heart disease with calcific aortic stenosis and congestive failure.

Atabrine has also been administered to a case of Fiedler's myocarditis with auricular flutter, 4:1 block, and left bundle branch block. Digitalis and quinidine were also administered without affecting the rhythm or the fatal outcome on the third hospital day.

DISCUSSION

This paper is presented as a preliminary report stressing the usefulness of atabrine in auricular fibrillation as an alternative to quinidine. Admittedly the series is too small for conclusive remarks; but it is nevertheless significant in that atabrine was effective in restoring regular sinus rhythm in four of eight cases of auricular fibrillation.

It was suggested by Nahum and Hoff[19] that the circus movement responsible for auricular fibrillation is the result of vagal stimulation superimposed upon an exciting factor (E). The latter included many conditions such as thyrotoxicosis, acute infections, and stretching of the auricular fibres during congestive failure which produces hyperexcitability of the myocardium similar to that seen in skeletal muscle and nerve tension.[20] From the foregoing it is reasonable to assume that the maximal effect of a drug would occur when both the vagal and E factors are at a minimum, such as might occur in mild hyperthyroidism, slight infection, or early congestive failure. These latter may be considered optimal conditions for anti-fibrillation therapy.

It must be admitted that the results reported in this paper are open to criticism, for it may be argued that the auricular fibrillation which occurred in the four successful cases was of the transitory type and would have remitted spontaneously. While one cannot deny the validity of such an objection, it is difficult to reconcile this with the fact that the auricular fibrillation in these cases remitted to regular sinus rhythm at a time coincident with the higher blood levels of atabrine. This fact will be alluded to subsequently. Furthermore in case 1 atabrine did restore regular sinus rhythm to the prevailing auricular fibrillation. When this arrhythmia recurred three days later it was again remitted to regular sinus rhythm by atabrine and remained at such when the patient was placed on maintenance doses of atabrine for several days. Thus, in keeping with the evidence submitted above it is reasonable to assume that atabrine was responsible in remitting auricular fibrillation to regular sinus rhythm in the four cases reported in this communication.

It may be noted that in those instances in which atabrine failed to restore regular sinus rhythm, quinidine and digitalis were also ineffective. On close analysis of the cases presented it can be seen that successful therapy occurred only in those cases falling into the category of optimal conditions. When Wenckebach[21] first introduced quinine for the treatment of auricular fibrillation, he reported no success in fibrillation of several years' duration. Case 5. closely parallels the type of refractory cases of auricular fibrillation reported by him, for while heart failure was not severe, auricular fibrillation was of long duration. Furthermore such cases are not amenable to quinidine therapy either.[22]

It is felt that atabrine may have a distinct advantage over quinidine. In intramuscular dosage of 0.4 gm., atabrine reaches a maximal blood level of 60 to 220 gamma/litre within one hour and falls to levels of 60 to 150 gamma/litre in three hours.[23] The maximal effect should therefore occur early. Thus in unselected cases of auricular fibrillation one may know in three or four hours, instead of waiting twelve to fifteen as with quinidine, whether or not response is to be expected. In such instances, search for another drug such as digitalis may be begun at an earlier hour.

SUMMARY

1. The use of atabrine in auricular fibrillation of short duration is suggested.

2. In the cases in which therapeutic failure occurred with atabrine, quinidine and digitalis, if not given previously, were also ineffective.

REFERENCES

1. LEWIS, T.: The Mechanism and Graphic Registration of the Heart-Beat, Shaw & Sons, London, 1925.
2. LEWIS, T., DRURY, A. N., ILIESCU, C. C. AND WEDD, A. M.: *Heart*, 9: 55, 1922.
3. LEWIS, T., DRURY, A. N., WEDD, A. M. AND ILIESCU, C. C.: *Heart*, 9: 207, 1921.
4. WEALSH, H. AND NACHMANSON, D.: *Proc. Soc. Exp. Biol. & Med.*, 54: 336, 1944.
5. MELVILLE, K. AND BABKIN, B. P.: (In press).
6. BABKIN, B. P. AND KARP, D.: *Canad. M. A. J.*, 56: 137, 1947.
7. CHIN, K.: *Japan. J. Med. Sc. IV, Pharm.*, 10: 162, 1937.
8. HARVEY, A. M.: *J. Physiol.*, 95: 45, 1939.
9. SUFFOLK AND BERKSHIRE, EARL OF: *Quart. J. Exp. Physiol.*, 29: 1, 1939.
10. MELVILLE, K. AND BABKIN, B. P.: (In press).
11. BABKIN, B. P. AND RITCHIE, T. W.: *Rev. Canad. de Biol.*, 4: 346, 1945.
12. GERTLER, M. M. AND KARP, D.: *Rev. Canad. de Biol.*, (In press).
13. *Idem*: *Proc. Soc. Exper. Biol. & Med.*, (In press).
14. *Idem*: In preparation.
15. GANGULI, P.: *Arch. f. Schiffs und tropen Hygienie*, 37: 413, 1933.
16. HEIMANN, H. L. AND SHAPIRO, B. G.: *Brit. Heart J.*, 5: 131, 1943.
17. SMITH, H. L. AND STOECKLE, J. D.: *Proc. Soc. Exp. Biol. & Med.*, 62: 179, 1946.
18. GERTLER, M. M., HOFF, H. E. AND HUMM, D. G.: *Am. J. Physiol.*, 146: 478, 1946.
19. NAHUM, L. N. AND HOFF, H. E.: *J. Am. M. Ass.*, 105: 254, 1935.
20. BEST, C. H. AND TAYLOR, N. B.: Physiological Basis of Medical Practice, Williams and Wilkins, Baltimore, 1944.
21. WENCKEBACH, K. E.: Die Unregelmassige Herztatigkeit und ihre Klinische Bedeutung, W. Engelman, Leipzig, 1914.
22. FAHR, G.: *J. Am. M. Ass.*, 111: 2268, 1938.
23. SHANNON, J. H.: *J. Pharmacol. & Exper. Therap.*, 81: 307, 1944.

AN ANALYSIS OF 115 CASES OF PERTUSSIS TREATED WITH PERTUSSIS ANTITOXIN

Ernest M. Worden, M.D.

Montreal, Que.

THERE is a very definite need for a specific serum in the treatment of whooping cough. At the present time, we have available for use in the treatment of active cases both human and rabbit serums. These are anti-bacterial alone or both anti-bacterial and antitoxic.

Bullowa and Alterman[1] have reported the effect of a rabbit antitoxin (prepared by immunizing rabbits with a special antitoxin) on cases of whooping cough. They felt it was of little value in treatment.

Bradford, Brooks and Katsampes[2] have used an antibacterial pertussis rabbit serum prepared by immunizing rabbits with H pertussis organisms. They felt that when used in conjunction with sulfadiazine the serum had a very definite value.

Hyperimmune antibacterial human serum has been used by many investigators. Scheinblum and Bullowa[3] reported on a series of 23 children suffering from whooping cough who received from one to four, 20 c.c. doses of the lyophile human serum; 52% of these cases showed a good, and 26% a moderate response. McGuinness, Armstrong and Felton[4] using the same serum reported an excellent result in 38.5% and a good result in 31.7% of active cases.

Lapin[5] has recently reported the use of a new globulin fraction of hyperimmune antibacterial pertussis human serum in 25 active whooping cough cases; 44% showed marked improvement, 28% showed moderate improvement and 28% no improvement.

During the two and a half year period between January, 1943 and June, 1945, we were afforded the opportunity of studying the effect of pertussis antitoxin on 115 clinical cases of pertussis. This study was carried out at the Alexandra Hospital for Infectious Diseases in Montreal. The antitoxin for the study was kindly provided for our use through the courtesy of the bacteriology department of Messrs. Ayerst, McKenna & Harrison.

A word of introduction about the antitoxin employed would perhaps be in order: This material is really a combination of an anti-endotoxin and an antibacterial serum. It is prepared by the injection into rabbits of two substances: (*a*) bacterial vaccine and (*b*) pertussis endotoxoid. The rabbits respond rapidly to the bacterial vaccine and in two or three weeks' time have produced a serum with titres up to 1 in 25,000. The response to the endotoxoid is however, much slower, usually taking two or three months. At the end of this time the animals are bled by intracardial puncture. The serum is separated and the globulin factor is precipitated and reconstituted to about one-eighth to one-quarter the volume. Protective tests are carried out on mice by inoculation with two M.L.D.s of toxin and then protecting them with graded dilutions of serum. The product is put up in vials containing 10,000 units. A unit represents the antitoxin material which will neutralize one skin test dose of pertussis toxin.

The present series of 115 cases represents only a small proportion of the total number of cases of whooping cough admitted over the two

and one-half year period. In all, 581 cases were admitted for treatment and the 115 cases represents a selected group. No case was selected for treatment if the child had signs of the disease for more than two weeks and only the most severe cases were included. These criteria were selected to give the treatment a severe yet fair trial. It was very difficult in some cases to get an accurate date of exposure or date of onset and so the duration of the illness before the child was admitted to hospital was difficult to determine with any degree of certainty. However, cases that were well-advanced were not treated because the normal course of events would be a gradual improvement and a falling-off of the number of spasms.

A routine physical examination, urinalysis, white blood count and smear were done on all patients. Clinically all patients had whooping cough; unfortunately, in only a small percentage of cases was the disease proven bacteriologically as we had difficulty in isolating the organism due to overgrowth with other bacteria commonly found in the nose and throat.

In attempting to evaluate the results of treatment it was felt that the most logical method was to observe the effect of treatment on the number and severity of the paroxysms of coughing. The pulse rate and temperature were of no value as these are normal in uncomplicated cases. Some workers have used the white blood count in judging the results of treatment but this seemed unsatisfactory as many of the very severe cases had only moderate leucocytosis and some of the very mild cases had very high counts. In a like manner, some of the investigators have used the changes in the hilar markings seen in routine chest films as an indication of the effect of treatment. This seemed to be rather indefinite and inaccurate.

Following admission each child was observed for a period of two to four days and during this time an accurate count of the number of spasms and their severity for each twenty-four hour period was made. When an approximate base line had been established 1/20 c.c. of the antitoxin was given intradermally as a sensitivity test; if this was negative a full dose of 10 c.c. of antitoxin (10,000 units) was given intramuscularly. A daily record of the number and severity of the spasms was then kept and charted for the balance of the child's stay in hospital.

Of the 115 cases only 4 showed a slight febrile reaction to 101° or less following the serum administration. In all cases the temperature returned to normal in 24 hours. One case developed an urticarial eruption with slight fever ten days following the injection of the antitoxin. The leucocyte counts varied between 9,900 and 80,000 with the majority being between 20,000 and 40,000. In all cases there was a predominant lymphocytosis except when a secondary complication was present.

The ages of the children studied varied between 4 weeks and 11 years. Thirty-six cases (31%) were under 6 months of age and 67 cases (58%) were under two years of age.

In the average untreated case of whooping cough the spasmodic coughing lasts about six weeks. For the first ten days to two weeks there is a gradual increase in the number of spasms and their severity, and for the last ten days or two weeks there is a gradual falling off of the spasms.

The effect of the antitoxin on the spasms varied widely and in order to present a complete picture of the different reactions obtained, the cases were divided into seven distinct and separate groups.

Group 1.—Cases showing a good response to antitoxin with lessening of the number and

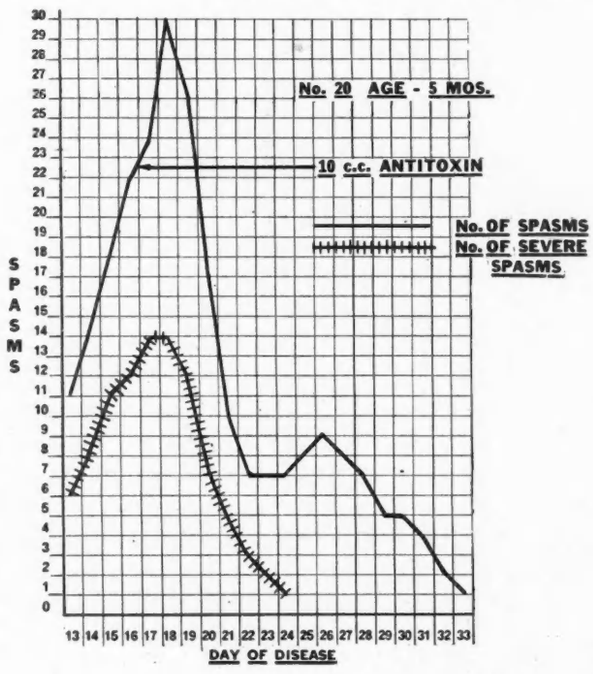


Fig. 1. Showing a dramatic response with lessening of the coughing spasms following administration of a single dose of antitoxin.

severity of the spasms. No further treatment was necessary. Thirty-four cases (29.5%) fell into this group and this represented the largest single group of cases. In some cases the effect of the serum was dramatic (see Fig. 1) while in others there was a more gradual response (Fig. 2).

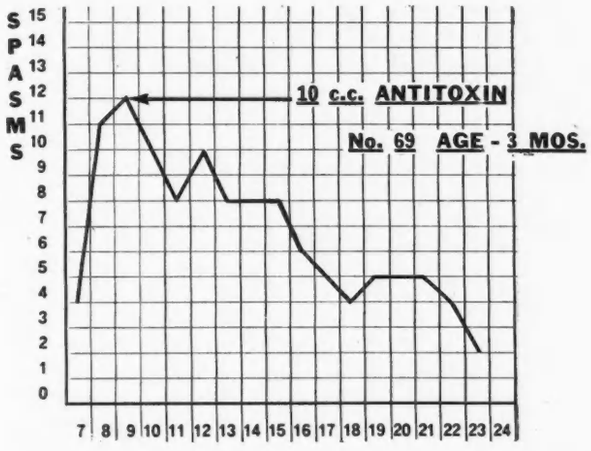


FIG. 2. A DEFINITE RESPONSE FOLLOWING ADMINISTRATION OF A SINGLE DOSE OF ANTITOXIN.

Group 2.—Cases showing a good initial response to antitoxin followed by a recurrence of spasms some days later. No further treatment was given. In this group there were 17 cases (14.8%). Fig. 3 represents such a case.

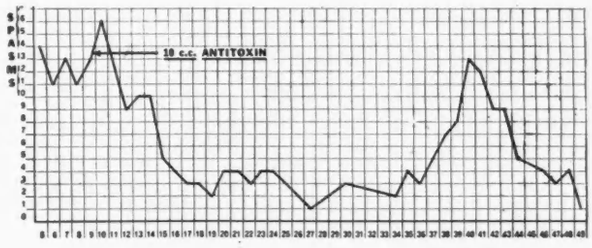


FIG. 3. SHOWING A PROMPT RESPONSE TO ANTITOXIN FOLLOWED BY AN INCREASE IN THE COUGHING SPASMS 2 WEEKS LATER.

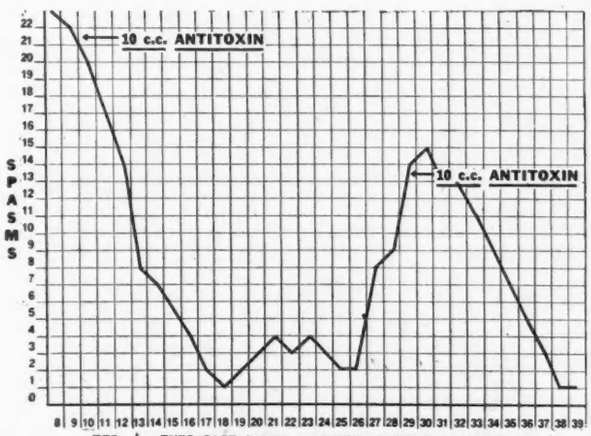


FIG. 4. THIS CASE SHOWS A MARKED INITIAL RESPONSE TO ANTITOXIN FOLLOWED BY A RECURRENCE OF SPASMS AND A SECOND PROMPT RESPONSE WITH THE SECOND DOSE OF ANTITOXIN.

Group 3.—Cases showing a good initial response to antitoxin, then a recurrence of spasms followed by a second good response when antitoxin was given a second time. There were 6 such cases (5.2%). Such a case is well illustrated in Fig. 4. Some of the cases in group 2 might well have fallen into group 3 had a second dose of antitoxin been given.

Group 4.—Cases showing a very slight but nevertheless definite response to antitoxin; 19 cases (16.6%) fell into this group (see Fig. 5).

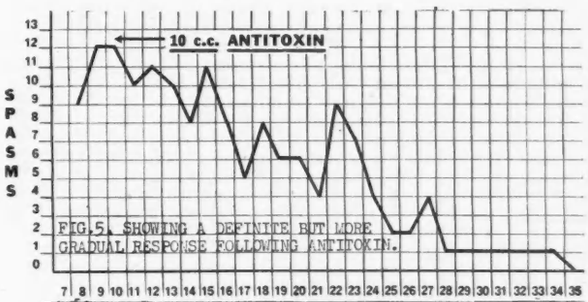


FIG. 5. SHOWING A DEFINITE BUT MORE GRADUAL RESPONSE FOLLOWING ANTITOXIN.

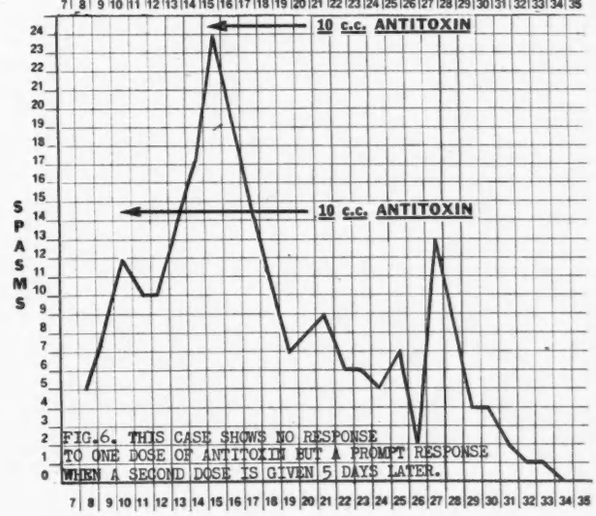


FIG. 6. THIS CASE SHOWS NO RESPONSE TO ONE DOSE OF ANTITOXIN BUT A PROMPT RESPONSE WHEN A SECOND DOSE IS GIVEN 5 DAYS LATER.

Group 5.—Cases which showed no response to one dose of antitoxin but showed a good response when a second dose was given 2 to 4 days later. This group comprised 13 cases (11.3%) (see Fig. 6).

Group 6.—Cases showing no response to a single dose of antitoxin. There were 17 cases in this group (14.8%). Fig. 7 illustrates such a case. Some of these cases might have fallen into groups 5 or 7 had a second dose of antitoxin been given.

Group 7.—Cases in which there was no response to two or more doses of antitoxin; 9 cases fell into this group (7.8%) (see Fig. 8).

Of the 26 failures in groups 6 and 7, eleven (42%) were in infants under one year of age and in the total series 51 cases (44%) were in

the same age group. This fact disproves a previous impression that the antitoxin was more effective in very young infants.

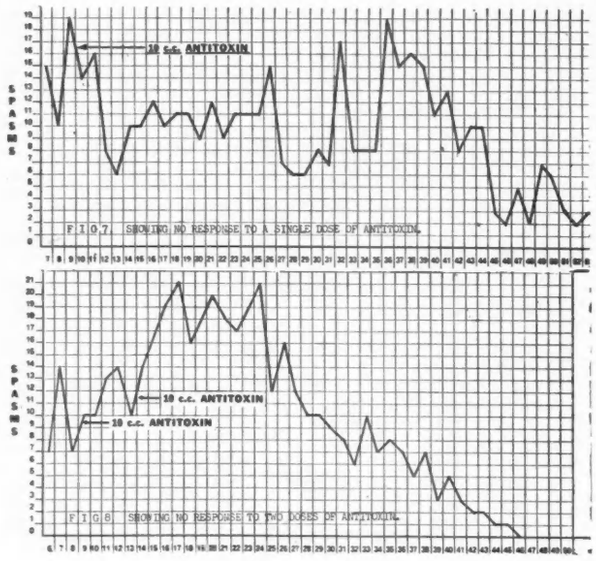


FIG. 7. SHOWING NO RESPONSE TO A SINGLE DOSE OF ANTITOXIN.

FIG. 8. SHOWING NO RESPONSE TO TWO DOSES OF ANTITOXIN.

EFFECT OF ANTITOXIN ON COMPLICATIONS

In the cases studied 28 (24.3%) developed pneumonia during their stay in hospital. Of these complicated cases 57% had pneumonia on admission to hospital or developed it in hospital prior to the administration of antitoxin. The remainder (43%) developed pneumonia after the administration of serum. In other words, 10.5% of all the cases developed pneumonia after the serum administration. This compares with an incidence of pneumonia of 11% in all cases of whooping cough admitted to hospital during 1940 and 1941, and in which no specific treatment was given. This, however, is hardly a fair comparison, as the cases studied in this present report represented the most severe cases admitted. Of the 28 pneumonia cases, 13 (42%) were infants under 6 months of age and 20 (71%) were under two years. There were 8 cases (69%) which developed catarrhal otitis media. All the complicated cases were treated with chemotherapy or penicillin or both and all made an uneventful recovery. No deaths occurred among any of the cases studied.

In all the cases in which antitoxin lessened the number and severity of the spasms, the spasms of coughing were not, however, eliminated completely and the children continued to cough for 2 to 4 weeks longer, having one or two mild spasms in each 24 hour period.

CONCLUSIONS

In the cases studied, by far the greater number showed a beneficial result following the administration of pertussis antitoxin. The degree of response and the amount of antitoxin necessary to produce a response varied as has been shown; 23% of the cases showed no response whatever to treatment while in the other case (77%) the effect varied from excellent to fair depending on the dosage used and the individual case.

The length of stay in hospital was not appreciably different from those cases receiving no specific therapy.

The incidence of pneumonia, by far the commonest complication, was the same as in a large group of untreated cases.

Antitoxin did not seem to be more effective in the younger age group but there was a similar variation in response in all age groups.

It would seem, therefore, that in pertussis antitoxin we have a valuable aid in the treatment of whooping cough. It is not helpful in every case but in the majority of cases if given in the first two weeks of the illness there will be a definite clinical improvement.

When secondary infections occur (bronchopneumonia, otitis media, etc.) chemo-therapy and penicillin are of very great value. Careful nursing care is still of the utmost importance in caring for these children. In a series, such as the one studied, the fact that there were no deaths speaks well for the treatment employed. No single factor is responsible, but certainly good nursing care, specific antitoxin and the use of chemo-therapy and penicillin when indicated seems to offer hope for a speedy and complete recovery from this most serious disease.

REFERENCES

1. BULLOWA, J. G. M. AND ALTERMAN, J.: *J. Am. M. Ass.*, 120: 883, 1942.
2. BRADFORD, W. L., BROOKS, A. M. AND KATSAMPES, C. P.: Quoted from Lapin. (5)
3. SCHEINBLUM, I. E. AND BULLOWA, J. G. M.: *J. Pædiat.*, 25: 49, 1944.
4. MCGUINNESS, A. C., ARMSTRONG, J. G. AND FELTON, H. M.: *J. Pædiat.*, 24: 249, 1944.
5. LAPIN, J. H.: *J. Pædiat.*, 26: 555, 1945.

In youth acquire that which may requite you for the deprivations of old age; and if you are mindful that old age has wisdom for its food, you will so exert yourself in youth that your old age will not lack sustenance. —Leonardo da Vinci.

EARLY AMBULATION IN THE PRACTICE OF OBSTETRICS

E. Cullen Bryant, M.D.

Toronto, Ont.

THE modern practice of early ambulation of surgical patients, now widely practised and accepted throughout America and parts of Europe, is intimately related to the practice of early rising in the puerperium. Though early ambulation is practised more widely in surgery than in obstetrics, surgery cannot take the credit, for the first known publication on early ambulation after surgery was that of Emil Reis of Chicago, who reported in 1899 on a series composed principally of vaginal repairs.

Charles White of Manchester wrote in 1793:

"The Parturient should be very high with head and shoulders, and should sit up in bed many times a day—and should kneel whenever she has occasion to make water, which should be done often. The frequent upright posture is of the utmost consequence and cannot be too strongly endorced. It prevents lochea from stagnation and stools and urine from being too long retained, and promotes the contraction of the uterus, together with that of the abdominal muscles. The sooner she gets out of bed after her delivery, the better, even on the same day if possible. She should not deter it beyond the second or third day at the farthest. . . ."

Greenhill (1944) writes:

"Beginning about 20 years ago, I gradually cut down the number of days my obstetrical and gynæcological patients remained in bed. Now I have progressed so far that, if my obstetrical patients cannot urinate spontaneously eight to ten hours after delivery and are uncomfortable as a result of full bladder, I have the patient helped out of bed to go to the toilet if there is one in the room. Naturally women who have bled a great deal and have had complications are not permitted to do this, but at least 90% of these women could be permitted out of bed on the first day without harm."

Physicians generally have frowned upon the idea of permitting a woman to get out of bed too soon after delivery, because of: (1) fear that the episiotomy would break down; (2) fear that there might be too much strain on the pelvic floor, resulting in prolapse and retroversion; (3) fear of post-partum hæmorrhage.

Recently, however, evidence has been collected to prove that early rising is beneficial to the patient. The fear of casualties during the London blitz (1940-1941) prompted obstetricians to allow their patients up in twenty-four hours and to go home on the third day. All reports show that no ill effects resulted from such treatment.

Stimulated by the success which has attended early ambulation of general surgical patients, with special reference to the work of Daniel Leithauser of Detroit (who first interested me in this practice), I was led to investigate the effects of similar treatment on women immediately after childbirth.

A total of 250 women were selected, between March, 1943, and December, 1946. A hundred and twenty-five patients delivered by myself were taken at random, and were patients who did not participate in early rising and were delivered prior to May, 1944, when I became interested in early rising and instituted it among my patients.

The other 125 cases were taken at random and delivered after May, 1944. There was no selection of cases. A routine was developed, which was used on all uncomplicated parturients. The exceptions included certain medical and surgical conditions, such as toxæmia and severe anæmia. Breech extraction and twins, the use of forceps, or episiotomy, were not considered contraindications.

The post-partum care for the two groups of patients did not vary essentially, except that in early ambulatory patients, an enema was substituted for the time-honoured castor oil, and a routine was developed in which patients would be up walking about by their 5th post-partum day.

The procedure and post-partum routine were as follows:

1. Ergot tartrate, tablet one, was given every four hours, after delivery for 24 hours.
2. A.P.C. & C. (two) were given for after pains, and repeated every two or three hours if necessary.
3. Mineral oil, oz. 1, given night and morning starting on the second P.P. day, for two days.
4. An S.S. enema was given on the 4th day if the patient had no bowel movement.
5. The patient was allowed to stand, encouraged to cough on the 1st P.P. day (if the patient was delivered before 4 a.m., it would be considered her 1st P.P. day, and if she were delivered after 4 a.m., she did not get up until the 2nd P.P. day). The patient was allowed and encouraged to move about on the bed, encouraged to lie on her stomach and was offered a light diet.
6. On the second P.P. day, she sat in the chair for five minutes.
7. On the third day the patient was allowed up, to sit in a chair and encouraged to walk.
8. Her perineum was irrigated with ½% lysol every six hours until discharged. The patient was taught as soon as possible to do this herself and each patient had her own individual dish with dressings.
9. If the patient had an episiotomy, light was applied twice a day for thirty minutes and sutured areas were painted with metaphen. If the sutures did not look well and showed any sign of suppuration, sulfathiazole was powdered about them.
10. The patient was allowed to go to the bathroom if there was one in her room, on the second P.P. day, but must be accompanied by a nurse. Ambulation must be gradual, and by the fifth day the patient is pretty well up at will. They were encouraged to pass their own water, but if necessary, were catheterized. This was followed by irrigation with boracic solution.

11. If her Hbg. was under 70%, ferrous sulphate gr. 5 were prescribed three times a day.

12. A light diet was prescribed as soon as the patient tolerated it, and full diet was given after the first movement, which was usually about the third day.

13. Fluids were pushed, the patient was encouraged to take eight to ten glasses of water, fruit juices, or milk daily.

14. The patient was encouraged to lie on her stomach on the second day, starting at ten minutes, then twice daily and gradually increasing.

15. On the fourth day she was shown how to do the knee-chest position or whatever exercises were instituted and she starts at these on the fourth day.

16. If the patient had had sutures, no attempt was made to have her take exercises, such as the knee-chest position, until after the sixth P.P. day.

17. For the repair of episiotomy No. 0 chromic catgut was used throughout, excepting the skin which was closed by interrupted sutures of dermol. The dermol was removed on the 7th or 8th day, according to when the patient was to leave hospital and how well the skin was healed.

TABLE I.
RESULTS

	Early	*Late*
No. of cases	125	125
Day out of bed	2.1	9.7
Day of discharge from hospital	9.1	10.9
Home by ambulance	0	8
Type of delivery:		
Spontaneous	73	69
Breech	5	4
Section	3	2
Low forceps	45	49
Twins	0	1
Average age	27 plus	25

It is to be noted that in the early risers the first day out of bed is 2.1%. This is because, first, of the lack of nurses and the numerous changing of nurses in the ward, some patients did not get out of bed until the 3rd day, and, secondly, a few patients (very few) would not get up on the 1st or 2nd. Also, three Cæsarean sections are included which did not get up until their 6th or 8th day.

There was no patient in the early ambulatory group who did not either go home by car or taxi, while in the late groups, although their stay in hospital averaged nearly 2 days longer, there were 8 patients that had to go home by ambulance. As to the method of delivery, they averaged pretty much the same. The high percentage of forceps deliveries is present because it has been my practice to use them in primiparæ (control forceps delivery) in a great majority of cases.

The Cæsarean section ratio was low, 5 in 250, or 2%.

The cases include primiparæ and multiparæ women. The average age is interesting because in the group of late risers, those delivered before May, 1944 are 2-plus years younger than those delivered after May, 1944, and may have something to do with the return of army personnel from overseas.

TABLE II.

	Early	*Late*
No. of cases	125	125
Morbidity, temp. of 100.4 or over for 2 c. days	4	4
No. of patients catheterized	6.4	8.57
Voluntary bowel mov't	102	43
Bowel mov't by enema	19	3
Bowel mov't by oil and M. of M	4	79
Healing—perineum	3 req. tr't'mt	3 req. tr't'mt
Involution	0 poor	4 poor
	1	1
	Offen. odour	Offen. odour
	1	1
	lochia lessened	mod. red. dis.
Feeding: Breast	111	100
Formula	14	25
Retroversion	19	29

In each series there were 4 patients who had a temperature of 100.4° for 2 consecutive days or over, and 7 in the early group that had intermittent temperatures. A perusal of the charts could not attribute the temperature in any way to early ambulation, as in these cases there were 1 prolapsed cord; 1 placenta prævia; 1 retained placenta with manual extraction, etc. No difference could be noted in the morbidity of the patients whether they got up early or late.

There was some appreciable difference in the catheterization rate but no attempt was made to measure residual urine.

The most striking result was in the bowel movements. In the early risers 102 women had had a bowel movement before the 4th P.P. day, and only 23 required enemas or oil, while, on the other hand, only 43 late risers had voluntary bowel movement before the 4th day and 79 required oil.

Involution was definitely better and in a more comprehensive study of the lochia, I believe there would be the same striking results.

The idea that early rising might predispose to prolapse and retroversion is here disproved, for in the early risers only 19 had retroversion six weeks after delivery.

Stander says that 41% of women, 6 weeks after confinement, show retroversion. As to feeding, it does not appear that early rising affects the flow of milk in the initial stages, as only 14 out of 125 babies left the hospital on formula, while in the late risers there were 25 out of 125. However, in speaking of breast-fed babies, they include those babies that are solely

breast-fed, or breast-fed with supplement. The nursery supervisor says that in order to maintain weight she has increased the strength of the supplement. Whether early rising does something to the milk concentration or not I am not prepared to say, but it would make an interesting study. One thing I do believe is that early ambulation seems to stimulate the flow of milk.

In those cases there were no complications such as phlebitis, embolism, etc., but one patient did have a moderate hæmorrhage on the 5th day, with no serious results.

On going through one of the large American hospitals where early ambulation is practised, I asked the supervisor if they had any late P.P. hæmorrhage, and she said, "Oh yes; there is the odd case that bleeds, but we feel that if they are going to bleed, this is the place to do it, not at home".

Conclusions from my own experience.—(1) Early rising results in more rapid and comfortable convalescence, with less asthenia and less postoperative and post-partum depression. (2) Less medication and rectal treatment is required. (3) Less nursing care with simplified P.P. care. (4) There is far more rapid return to normal body function. (5) The improvement in morale is tremendous and the majority of the patients have been in favour of this form of treatment and desire it for the next confinement. As far as my practice is concerned, it has doubled since the inception of this procedure. (6) There is no delay in the healing of perineum or any deleterious effects. (7) The incidence of retroversions is decreased. (8) Postoperative invalidism is reduced and there are less complications. (9) The home convalescence is decreased and the woman is better able to carry on her duties. This is very important in these times when domestic help is so difficult to procure.

Early postoperative rising is not a blanket formula and all patients do not benefit by it.

Contraindications.—(1) Prolonged preoperative bed rest, as in cardiac insufficiency. (2) Serious anæmia and shock. (3) Retained placenta. (4) Hæmorrhage. (5) Presence (or suspected presence) of thrombi. (6) Long, difficult deliveries. (7) Cases in which infection is suspected.

If ambulation is to be undertaken, the importance of its being carried out in detail cannot be overemphasized. (1) The patient must be up walking, not sitting. (2) The best time is 24 to 36 hours P.P., and the best time to act and prevent a difficulty is before it arises. It is known that many postoperative complications are apparent in a patient during the first 24 to 36 hours. (3) Later than the 3 or 4 days, few benefits are obtained and it is better to keep them in bed.

If there is not complete agreement amongst all observants, those that have tried early ambulation are convinced that it has many advantages. The functions of the body, both in health and disease, depend upon efficient respiration, circulation, digestion, and elimination of wastes. It is known that these functions are temporarily disturbed as a result of confinement, anæsthetic, prolonged labour, and prolonged immobility in bed. Lack of exercise of the chest muscles and impaired pulmonary metabolism leads to lessened vital capacity, circulation stagnation, shock, thrombosis, phlebitis, and embolism. Intestinal and muscular atony from inactivity prolongs the period of recovery and undermines the patient's general health and depresses her morale.

Workers, especially those in Boston, have shown that the vital capacity is greatly reduced with bed rest and it takes considerable time to get back to normal, while if one institutes early ambulation, the vital capacity comes back to normal much more quickly and thus the normal body functions are at the same time restored.

BIBLIOGRAPHY

1. WHITE, C.: Treatment in Management of Pregnant Women and Lying-In Women, 1793 (Worcester, Mass.).
2. ROTSTEIN, M. L.: *J. Am. M. Ass.*, **125**: 838, 1944.
3. ROSENBLUM, G.: *J. Am. M. Ass.*, **129**: 849, 1945.
4. KING, A.: *J. Obst. & Gyn.*, October, 1946.
5. STEINHART, P. F.: *Surg., Gyn. & Obst.*, **82**: 348, 1946.
6. LEITHAUSER, D. J.: Early Ambulation and Related Procedures in Surgical Management, Charles Thomas, 1946.
7. HALL, J. E.: *Brooklyn Hosp. J.*, January, 1947.

It is one of the peculiarities of medical superstition that it attributes every ordinary and natural effect to extraordinary and unnatural causes; thus we find in the times of superstitious delusion that even the salutary effect of well known herbs were attributed to the influence of the planet under whose ascendency they were collected, rather than any intrinsic property in the herb itself.—William Wadd.

THE ISOLATION OF HERPES SIMPLEX VIRUS FROM A CASE OF POLIOENCEPHALITIS*

James W. Fisher, M.A., M.Sc., Ph.D.

Ottawa, Ont.

and

John W. Patrick, M.D.

Montreal, Que.

IN the summer of 1946, poliomyelitis was epidemic in several centres in Canada.[1] In Montreal a few isolated cases occurred about the middle of June. The peaks of high frequency were reached in the second and fourth weeks of August, and by the end of October only a few sporadic cases were observed.[2] Towards the end of July there was admitted to Queen Mary Veterans' Hospital, Montreal, a patient, the differential diagnosis of whose illness at that time was either polioencephalitis, acute tuberculous meningitis or a brain abscess. The purpose of this paper is to report the isolation of a strain of herpes simplex virus from the spinal fluid of this individual.

CASE HISTORY

Patient G.M., male of 25 years of age, was admitted to hospital shortly before midnight July 29, 1946. He had a history of a headache of one week's duration, drowsiness one day and was semi-comatose since 3.00 p.m. of the same day. The only past history of significance was earache two weeks previously, for which irrigation had been carried out.

When first seen the patient was lying in a comatose condition while his body was held in a position of generalized flexion. He was extremely restless. His face and neck were cyanotic. With the exception of photophobia and sluggish, moderately dilated pupils, examination of the cranial nerves showed no abnormality. There was generalized hyperæsthesia, moderate neck rigidity and a slightly positive Kernig's sign. All reflexes were present and bilaterally equal. The temperature was 104.0° F. (rectal), the pulse 88, the respiration 22. The blood pressure was 126 systolic, 70 diastolic.

On July 30, at 2.30 a.m., he had a generalized seizure which was not observed by anyone of authority, but it was stated that he became exceedingly restless, moved up on his hands and knees while his entire body shook; the head turned in both directions and his eyes remained closed. A lumbar puncture performed shortly afterwards gave a clear colourless fluid with an initial pressure of 155 mm. (water). A second puncture later in the morning revealed 260 monocytes and 30 polymorphonuclear leucocytes. By that afternoon there was an apparent cerebral involvement more of a generalized nature than meningeal. The patient was extremely irritable and incontinent of urine.

The laboratory report at this time was: x-rays of chest and skull, negative; blood, 15.6% hæmoglobin, 11,400 white blood cells per c.mm.; differential count, 80% polymorphonuclear leucocytes (5% stab forms, 75% segmented), 12% small leucocytes, 6% large lymphocytes, 2% monocytes; toxic granulations of polymorphonuclear leucocytes, reported; non-protein nitrogen, 33 mgm. %; urinalysis, negative.

The temperature remained elevated from 100 to 104° F. for two days. Symptoms suggesting severe cerebral irritation continued during this time. Coincident with the diminution of fever to within normal range was an improvement in his mental condition. He showed signs of response by July 31, and by the following day co-operated with the attendants. Complete normal conscious level was regained two days later, although moderate frontal headache persisted for an additional month. He was carefully followed by means of spinal fluid studies and it was not until 24 days after admission that the spinal fluid count returned to normal. When this occurred (August 26) an electroencephalogram demonstrated some increase in amount of slow wave activity in the frontal regions, but was insufficient to be considered pathological. A pneumoencephalogram the following day was negative. These two tests were made to rule out definitely the presence of a brain abscess. This was considered necessary in view of the history, although vague, of earache.

The patient feeling perfectly well except for occasional frontal headaches was discharged on September 23, 1946. Subsequent neurological examinations made at regular intervals have been entirely negative. No residual effects from his illness have been observed except for frequent frontal headaches.

VIRUS STUDIES

Two samples of spinal fluid were received. The first was taken on July 31, and the second on August 5. The former was diluted on receipt, and the latter before shipment, by the addition of an equal volume of 50% glycerol-saline solution buffered at pH 7.0 with 0.1 M. disodium phosphate buffer. Blood specimens were obtained on August 5, September 4, and the following April 2. Owing to circumstances beyond our control additional convalescent sera were not received. The specimens were shipped on ice and were about 3 hours in transit. On receipt the spinal fluids and the sera were distributed in small amounts and stored until used in sealed ampoules at −70° C. All specimens were bacteriologically sterile when tested by the usual bacteriological methods.

Preliminary observations. — On August 6, aliquot portions of the spinal fluid specimens were pooled and tested for presence of virus by their application to the lightly scarified corneal surfaces of 2 rabbits, and by intracranial injection into 2 guinea pigs and 2 groups of 6 mice at dilutions of 1:2 and 1:100 (Table I). The cornea of one of the rabbit's eyes to which the 1:100 dilution of material was applied was very slightly clouded between the 3rd and 4th days after which it cleared. As suggested by Steigman and Scott[3] a bacteriologically sterile extract was prepared from the nictitating membrane on the 4th day and passaged intracranially into groups of 6 mice at 5 levels having a log difference of 0.3 and starting at a 1:10 dilution. No evidence of infection was observed up to a period of 3 weeks at which time these animals came off test. When challenged intracerebrally

* From the Laboratory of Hygiene, Department of National Health and Welfare, Ottawa, and Department of Neurosurgery, Queen Mary Veterans' Hospital, Montreal.

TABLE I.

ANIMAL RESPONSES TO SPINAL FLUID SPECIMENS OF PATIENT G.M.

Animal No.	Pooled spinal fluids tested					Challenge test‡ (October 8, 1946)	
	Date, 1946	Volume	Dilution 1 in	Route	Result	Virus	Result
Guinea pigs							
1	August 6	0.15	2	Intracranial	Negative	G.M.	Abortive
2	" 6	"	100	" "	104.5—6th day	Bartleson	Resistant
3*	" 11	"	2	" "	104.5—6th "	"	"
4	" 11	"	"	" "	104.8—5th "	G.M.	Abortive
5*	" 11	"	"	" "	104.3—5th "	Bartleson	Resistant
6	" 11	"	100	" "	Negative	G.M.	Susceptible
7*	" 11	"	"	" "	104.0—7th "	Bartleson	Resistant
8	" 11	"	1,000	" "	Negative	G.M.	Susceptible
9*	" 11	"	"	" "	104.2—6th "	Bartleson	Resistant
10	" 11	"	10,000	" "	Negative	G.M.	Susceptible
11	" 11	"	"	" "	"	Bartleson	Susceptible
Rabbits							
1¶	August 6	0.1	2	Scar. rt. cornea	Negative	Bartleson	Susceptible
		"	100	" lt. "	Clouded (?)—3rd day Negative—4th day		
2	" 6	"	"	" rt. "	"	G.M.	"
		"	2	" lt. "	"		
3	" 11	0.3	"	Intracranial	104.6—4th day	Bartleson	Resistant
4	" 11	"	"	" "	104.8—4th "	G.M.	"
5	" 11	"	100	" "	105.6—5th "	Bartleson	Abortive
6**	" 11	"	"	" "	105.4, Herpes—6th day		
7§	" 11	"	1,000	" "	104.8, Herpes—8th day		
8	" 11	"	"	" "	Negative	G.M.	Susceptible
9	" 11	0.1	2	Scar. lt. cornea	Clouded—24 hr.	G.M.	"
		"	100	" rt. "	Negative		
10	" 11	"	50	" rt. "	Clouded—36 hr.	Bartleson	"
			1,000	" lt. "	Negative		
11	" 11	"	100	" lt. "	Clouded—24 hr.	G.M.	"
			1,000	" rt. "	Negative		
12	" 11	"	2	" rt. "	Clouded—24 hr.	Bartleson	"
			50	" lt. "	" 24 "		
13	" 11	"	50	" rt. "	" 24 "	G.M.	"
			100	" lt. "	Negative		
Mice							
1 to 6	August 6	0.03	2	Intracranial	Negative	G.M.	0/6 Herpes
7 " 12	" 6	"	100	" "	No. 8 dead—5th day	Bartleson	2/4 "
13 " 22	" 11	"	2	" "	Negative	G.M.	1/10 "
23 " 32	" 11	"	"	" "	"	Bartleson	0/9 "
33 " 42	" 11	"	100	" "	"	G.M.	3/10 "
43 " 52	" 11	"	"	" "	"	Bartleson	1/10 "
53 " 62	" 11	"	1,000	" "	Nos. 53, 54, Herpes (?) 4th day	G.M.	0/8 "
63 " 72	" 11	"	"	" "	No. 63,§ Herpes—4th day	Bartleson	1/9 "
73 " 82	" 11	"	10,000	" "	Negative	G.M.	9/10 "
83 " 92	" 11	"	"	" "	"	Bartleson	10/10 "

* Immunized by subcutaneous and intra-abdominal injection of fresh mouse brain G.M. virus extending from August 21 to September 28, 1946.

¶ Negative intracranial passage of decimal dilutions of left nictitating membrane into mice.

** Negative intracranial passage of a 1:10 dilution of brain material into mice, guinea pigs and rabbits.

§ Positive intracranial passage of 1:100 and 1:1,000 dilutions of brain material into mice.

‡ Deaths attributed to herpes simplex viruses in challenge test control animals: Guinea pigs: 8 of 9 with Bartleson, and 10 of 10 with G.M. Rabbits: 4 of 4 with Bartleson, and 6 of 6 with G.M. Mice: 17 of 20 with Bartleson and 18 of 20 with G.M.

Negative, resistant = no clinical signs of infection, temperature less than 104° F.; abortive = temperature greater than 104° F. and/or signs of central nervous system infection but no death; susceptible = death preceded by signs of central nervous system infection.

104.5, temperature °F., rt., right, lt., left; 2/5 Herpes, deaths attributed to herpes simplex virus in 2 of 5 mice injected.

a week later with the Bartleson strain (*vide infra*) of herpes simplex virus, they and all the control mice showed signs of a herpes simplex infection and died. Of the animals injected intracranially, only those receiving the 1:100 dilution showed signs of infection: one guinea pig had a slight fever on the evening of the 6th and one mouse was found on the morning of the 5th day with its head partially eaten and its hind legs vigorously extended.

Isolation of virus.—In view of these preliminary observations an additional experiment, in which dilutions of 1:2, 1:100 and 1:1,000 of the pooled spinal fluids were injected intracranially into a larger number of animals, was carried out on August 11 (Table I). Between the 4th and 7th days, 5 of 9 guinea pigs and 3 of 6 rabbits had a fever only. One rabbit (No. 6) injected with a 1:100 dilution had an elevated temperature on the 6th day, ate and drank poorly and was hyperexcitable to external stimuli. An hour after the last observation it was found dead with hind legs extended; evidence of recent hypersalivation was present. Intracranial injection of a 1:10 dilution of an extract prepared soon after death from the brain of this animal, into 2 rabbits and 2 guinea pigs as well as 6 mice, produced no clinical signs of infection, other than a transient fever on the 6th day in both a rabbit and a guinea pig, up to a period of five weeks at which time they came off test. A second rabbit (No. 7) which had received the 1:1,000 dilution had the above-mentioned symptoms on the 8th day and when prodded went into a convulsion and died. Its brain was treated similarly and passaged intracranially at 1:10, 1:100 and 1:1,000 dilutions through the same number of mice, guinea pigs and rabbits. Of the mice, only 3 of 6 and 4 of 6 became ill in the respective groups that received the 1:100 and 1:1,000 dilutions; this occurred between the 4th and 7th days. They had ruffled fur, remained in a corner of the cage and had muscular twitchings. They were highly excitable and, from about 6 to 12 hours after the symptoms were observed, died with convulsions. These seizures could often be precipitated by swinging the animals by their tails. No difficulty was experienced in passaging the infectious agent from the brains of these mice at a 1:100 dilution through others by the intracranial route. All of the guinea pigs had a fever during the first and second weeks. One rabbit which received the 1:1,000 inoculum showed signs of a central nervous system infection and died on the 8th day, while in all the others for the most part only fevers were noted.

Only one group of mice that were injected with the original spinal fluids showed signs of infection. The inoculum in this instance was a 1:1,000 dilution. Three of the mice on the 4th day had the symptoms that have already been described. The next morning 2 were dead; 1 brain was bacteriologically sterile and from the other *Sal. enteritidis* was recovered. The 3rd mouse (No. 63) developed a marked tremor and 20 minutes later convulsed and died. Other mice injected intracranially with material prepared from the brain of this animal at levels of 1:100 and 1:1,000 developed illnesses of a similar nature whose incubation periods varied from 6 to 14 days, while the 1:10 dilution produced no visible effects. Subsequently the infectious agent was carried by serial intracranial passage through other mice; as well, it was adapted without difficulty to guinea pigs and rabbits by this route at a 1:1,000 dilution. In view of the fact that the inocula were bacteriologically sterile in each instance when infections were produced in the animals, it was assumed that a virus had been isolated although its filterability was not tested. Because the symptoms of the infections in the mice often simulated those of lymphocytic choriomeningitis, and since it was known that a small proportion of our stock mice carried this virus in the latent state, 60 control mice were inoculated with broth and a similar number with pooled brain material from 20 apparently normal mice. On no occasion was an infectious agent established.

TITRATION OF THE VIRUS

It was found on titrating intracranially the 3rd, 4th and 5th unbroken serial-brain passages of the virus from mouse No. 63 at decimal dilutions in groups of 10 mice of 21 days of age and of uniform weight, that the quantitative method of assay developed by Bliss and his associates[4, 5, 6] was not applicable owing to the marked variability of the number of deaths at the various levels. The use of probits in such a procedure employing vaccine, herpes and poliomyelitis viruses has already been described.[7] However, on the 6th passage only, a linear relationship between probit percentage mortality and the logarithm of the dose was obtained using 30 mice to a dilution. The slope of the regression line was of the order of 2; the RD_{50} (median lethal) dose was $10^{-4.2}$*. In subsequent passages and experiments lack of goodness of fit of the experimental points to the curves precluded this quantitative method of assay either of the virus alone or in the presence of serum. A similar difficulty was

* Titration of the virus that had been held under anaerobic conditions in sealed ampoules at −70° C. for a period of two months, often yielded an RD_{50} titre as low as about 1:100.

encountered with the Bartleson strain of herpes simplex virus. Accordingly, in all the titrations reported here an approximate value of the RD_{50} dose of virus was obtained by the method of Reed and Muench[8] which has the drawback that it gives no estimation of the standard error of the RD_{50} point.

ATTEMPTS TO ADAPT THE VIRUS TO THE CORNEÆ OF RABBITS

Application of a number of different concentrations of the spinal fluids to the lightly scarified surfaces of rabbits' corneæ was done in an attempt to adapt the virus to these animals by this route (Table I). None of the animals had a recorded temperature elevation or showed signs of infection suggesting an involvement of the central nervous system from the time they were inoculated until their immunity was challenged. However, definite local reactions invariably occurred only on those corneæ to which 1:2 and 1:50 dilutions were applied. From 24 to 36 hours following the inoculation an opacity of the cornea appeared which within 2 days well covered the entire surface. At about the time when the clouding was at a maximum, keratitis and conjunctivitis developed which was accompanied by a purulent discharge. The whole reaction lasted from about 7 to 10 days, at which time the inflammation subsided. The control animals for this experiment received similar dilutions of the spinal fluids which in this instance had been aerated for 6 hours at 37° C.,[9] and one concentration was applied to the corneæ of an animal. No clinical reactions were observed.

At a later date similar corneal reactions were produced in 9 rabbits in response to a 1:2 dilution of the spinal fluids which still contained viable virus as was demonstrated by their ability to produce herpetic deaths in rabbits in low concentrations. Six of the animals were on test for a period of 8 weeks during which time none of them showed signs of a central nervous system infection. The eyes of each of the others (R192, R193, and R194) were removed at daily intervals following the scarifications in an attempt to demonstrate corneal inclusion bodies.* The specimens were fixed in either Bouin's fluid or 10% formalin. They were stained by a variety of methods including hæmatoxylin-eosin, Giemsa, hæmatoxylin-safranin and eosin-methylene blue. The hæmatoxylin-eosin sections were of the greatest value from the viewpoint of histopathology while no significant difference in the sections was noted according to the fixative used.

The epithelial corneal injury in R192, from which the specimens were taken 24 hours following the scarification, had been repaired by a thickened layer of reduplicated, non-keratinizing stratified squamous cells which dipped downwards into the site of the lesions. A few polymorphonuclear leukocytes were scattered throughout the regenerated epidermis as well as in the corneal interstices. Following the cornea peripherally to the conjunctival reflection an acute inflammatory reaction was encountered beneath the corneal epithelium at a point corresponding with the base of the ciliary bodies. This reaction was characterized by œdema, hyperæmia and numerous inflammatory cells. The remainder of the eye was essentially normal and no inclusion bodies were demonstrable. In several of the specially stained sections the cytoplasmic granules of the polymorphonuclear leucocytes had assumed a strongly acidophilic character and under low power gave the false impression that inclusion bodies were present in the corneal epithelium. However, by careful examination under oil immersion it became obvious that the cells containing such bodies were actually polymorphous phagocytes which had wandered into the surface epithelium.

In the 48 hour specimens (R193) the corneal injury was difficult to detect, being represented by a small, localized area in which the superficial epithelium was somewhat flattened and showed a slight tendency to keratinization, while the laminæ of the underlying corneal stroma were infiltrated by a small, though fairly diffuse focus of polymorphonuclear leucocytes. Peripherally, however, and corresponding with a point roughly that of the conjunctival reflection, an acute inflammatory corneal reaction was encountered similar to that described with reference to R192. The ciliary body itself was also slightly hyperæmic and œdematous. In the third animal (R194) the point of corneal trauma was readily demonstrated, and its general characteristics resembled that of R192, except for the fact that fewer polymorphonuclear leucocytes were to be seen. For the most part, the conjunctiva clothing the cornea was slightly thinner than that of the other specimens, while the superficial epithelial cells showed a slight tendency to keratinization. Peripherally, the

* The following description of the histopathology is based upon a report of Dr. Max Klotz, Pathologist, Ottawa Civic Hospital, Ottawa, to whom we are indebted for this phase of the investigation.

inflammatory reaction as noted in the other specimens was less active; fewer cells were present and the œdema and hyperæmia appeared to have decreased.

IDENTIFICATION OF THE VIRUS

The G.M. virus produced in the animals clinical pictures which resembled those that have been described for various strains of herpes simplex virus.[10 to 14] However, the virus was finally identified by animal protection and cross neutralization tests in which a known strain, the Bartleson*, of herpes simplex virus and its homologous anti-serum were used. This strain had been subjected to 33 mouse passages before its receipt and 4 additional ones in this laboratory. Its LD_{50} titre was about $10^{-4.6}$.

The animals that survived the initial injection of spinal fluids were challenged for immunity with either the G.M. or Bartleson brain-passaged viruses. The strains of virus were homologous for the species of animal being tested, while the dilutions were 1:100. Four of the guinea pigs, however. had been subjected to a program of immunization with the G.M. virus that extended over a period of about a month, and 10 millilitres of blood were obtained from these animals 2 days before they were re-injected. The results of this experiment are given in Table I. It will be seen that the guinea pigs which were immunized with the G.M. virus, as well as certain rabbits and groups of mice that received the spinal fluids intracranially, demonstrated a high degree of immunity to an intracranial dose of the known strain of herpes simplex virus which regularly produced deaths in the control animals.

The neutralization tests were carried out in groups of 20 mice by a technique similar to the one recommended by the Neutrotropic Virus Disease Commission etc.[15] The viruses used were the intracranially passaged mouse-adapted G.M. and Bartleson strains, while the sera were obtained from the hyperimmunized guinea pigs. The neutralizing indices obtained are given in Table II, and indicate that the sera being tested possessed a definite neutralizing capacity for each of the strains of virus which were used.

The results, therefore, of both the animal protection and neutralization tests, seemed to demonstrate that the virus isolated in this laboratory was a strain of herpes simplex.

TABLE II.

NEUTRALIZATION TESTS IN MICE WITH KNOWN HERPES SIMPLEX (BARTLESON STRAIN) AND G.M. VIRUSES

Sera		*Virus G.M.*	*Virus Bartleson*
Anti-Bartleson		2,885*	3,800
Anti-G.M.			
Guinea pig No.	3†	800	1,200
" "	4	32	7
" "	5†	680	970
" "	6	5	11
" "	7†	723	600
" "	8	0	8
" "	9†	759	478
" "	10	18	14
" "	11	26	32
Rabbit No.	3	0	11
" "	4	14	22
" "	5	8	0
" "	8	6	4
" "	9 to 13‡	10	6
G.M.			
Blood drawn, Aug. 5, 1946		1,178	631
Blood drawn, Sept. 4, 1946		1,259	980
Blood drawn, Apr. 2, 1947		789	492

* Neutralization index.—Antilogarithm of (log LD_{50} of control—log of LD_{50} titre of serum). Indices of 1 to 9 are considered negative, 10 to 49, equivocal and 50 or more, positive.[15]

† Guinea pig numbers 3, 5, 7 and 9 were subjected to an immunization program with the G.M. virus. Specimens of blood were obtained from these and the other animals on October 6, 1946.

‡ Pooled specimen of serum prepared from equal amounts of each animal.

THE SOURCE OF THE VIRUS

The specimens of spinal fluid examined for virus were obtained from G.M. at a time when he had an acute attack of polioencephalitis. While herpes simplex virus has been employed during the past two years in these laboratories for experimental studies, on no occasion have we observed in our animals, in response to intracranial injection of other spinal fluids or materials from various sources, either clinical or immunological manifestations of infections resembling those which are caused by herpes simplex virus under conditions where they should not have occurred. Although lymphocytic choriomeningitis virus was recovered from 3 of a total of 150 control mice that received broth inocula during this investigation, the immunological pattern of the G.M. virus would preclude its identification as this type. The neutralizing indices of probable diagnostic significance,[15] which were obtained with the acute specimen of serum (Table II), seemed to demonstrate an appreciable level of neutralizing antibodies at the time the spinal fluids were tapped. This might be considered indicative of a comparatively recent herpetic infection. It is thus

* The Bartleson virus and serum specimens were obtained through the courtesy of Colonel J. E. Smadel, Scientific Director, Department of Virus and Rickettsial Diseases, Army Medical School, Washington 12, D.C.

assumed that the virus likely was human in origin.

DISCUSSION

The principle of using diluted spinal fluid specimens for the isolation of the G.M. virus is much the same as that used for demonstrating the presence of active virus in presumably neutral serum-virus mixtures,[16] but one which is not commonly employed in diagnostic procedures, Similarly, the interference effect,[17] which in some instances with influenza virus has been attributed to the presence of inactive virus particles, may be eliminated by dilution.[18, 19] It has been found preferable, therefore, to employ an inoculum of a low, rather than a high, virus concentration if the maximum yield of virus in eggs is to be attained.[20] It is also recognized that mutants may exist in animal[21] and plant viruses[22 to 24] as well as bacteriophages.[25] For the optimal propagation of certain of the latter a dilution of inoculum was used that would contain only an effective number of particles of the dominant mutant.[25] The dual nature of a presumably neurotropic strain of Western equine encephalomyelitis virus is considered to have been demonstrated by the "breaks"[26] which occurred in the dosage response curves;[27] by working subsequently at critical test dilutions two strains of this virus were separated which gave regression lines of statistically different slopes.[27]

Clinical herpetic infections in mice and rabbits were produced by intracranial injections of low concentrations of the spinal fluid specimens; on the other hand, the interference effect was encountered when attempts were made to adapt the virus in the spinal fluids to these animals at high concentrations. In the latter instance, only subclinical infections occurred in the three species of animals used, as evidenced by their subsequent high degree of immunity on challenge and the rises in temperature of the guinea pigs and rabbits. This immunity was probably of a cellular type since an appreciable level of circulating neutralizing antibodies at the time the animals were resistant could not be demonstrated. The suppression of virus propagation in some instances has been attributed to the presence of inactive virus in the inoculum.[18] On the present occasion, however, it is suggested that the agent which presumably caused this interference was one that was capable of producing an infection on the corneæ of rabbits as was demonstrated by the clinical reactions and the observations of histopathology. Thus, a tentative hypothesis is formulated to the effect that the virus isolated from G.M. was composed of two variants, each of which multiplied in two different types of host cells and which could be separated by dilution. In attempts to adapt human strains of virus to non-human tissues, should the presence of inactive virus in the inoculum interfere with the propagation of active virus of the same (or different) type, or one variant act similarly regarding another variant, then it might be considered advisable to take cognizance of the interference effect, virus variation and the host-cell-virus relationships.

There are only a few references in the literature which offer good evidence that herpes simplex virus may be the cause of human acute encephalitis.[11 to 14] As other authors have pointed out,[14] the subject in general is one of controversy.[10, 28] It has been reported that herpes simplex virus may be present in the oral secretions of apparently normal persons,[29] and "the etiological significance of the herpes (simplex) virus, when found in the brain or spinal fluid, has been questioned because of its occasional demonstration in the spinal fluid of individuals showing no evidence of encephalitis or herpetic eruptions".[11] It cannot be said definitely that the G.M. virus was the cause of the patient's illness, since a further increase in the already high level of circulating neutralizing antibodies was not demonstrated. It might have been that G.M. was infected earlier and at the time the spinal fluids were obtained a dominant neurotropic strain of herpes simplex virus was already present in them, because it was this strain that most readily could be adapted to animals by the intracranial route with subsequent manifestations of a central nervous system infection. Whether this virus was activated by some other stimuli to produce the encephalitis is difficult to say. It is worthy of note, however, that this illness occurred at a time when poliomyelitis was epidemic in the patient's community, and that there was little doubt in the clinician's mind as to whether this was a case of polioencephalitis.

SUMMARY

A strain of herpes simplex virus was recovered from high, rather than low, concentrations of pooled spinal fluid specimens, which were ob-

tained from an adult individual when poliomyelitis was epidemic in his community and he was suffering from an acute illness clinically diagnosed as polioencephalitis. A relatively high level of circulating neutralizing antibodies was present in the acute phase serum at the time the spinal fluid contained the virus. The lack of demonstrable further increase in the antibody titre precluded the laboratory diagnosis of disease due to herpes simplex virus. The significance of these observations is discussed.

REFERENCES

1. Dominion of Canada Bureau of Statistics: Summary of Cases of Notifiable Diseases in Canada, as Reported by the Provincial Health Departments, 1946.
2. GROULX, A.: *Bull. d'Hyg. Ville de Montréal*, **32**: 3, 1946.
3. STEIGMAN, A. J. AND SCOTT, T. F. M.: *The Lancet*, **1**: 761, 1942.
4. BLISS, C. I.: *Ann. App. Biol.*, **22**: 134, 1935.
5. *Idem*: *Ann. App. Biol.*, **22**: 307, 1935.
6. MILLER, L. C., BLISS, C. I. AND BRAUN, H. A.: *J. Am. Pharm. Ass.*, **28**: 644, 1939.
7. BONÈT-MAURY, P.: *Rev. canad. de biol.*, **5**: 489, 1946.
8. REED, L. J. AND MUENCH, H.: *Am. J. Hyg.*, **27**: 493, 1938.
9. PERDRAU, J. R.: *Proc. Roy. Soc.*, London, S.B., **109**: 304, 1931.
10. VAN ROOYEN, C. E. AND RHODES, A. J.: Virus Diseases of Man, Chapters 14 and 60, Oxford University Press, London, 1940.
11. SMITH, M. G., LENNETTE, E. H. AND REAMIS, H. R.: *Am. J. Path.*, **17**: 55, 1941.
12. ARMSTRONG, C.: *Pub. Health Rep.*, **58**: 16, 1943.
13. ZARAFONETIS, C. J. D., SMADEL, J. E., ADAMS, J. W. AND HAYMAKER, W.: *Am. J. Path.*, **20**: 429, 1944.
14. WHITMAN, L., WALL, J. M. AND WARREN, J.: *J. Am. M. Ass.*, **131**: 1408, 1946.
15. PAUL, J. R.: "The Filterable Viruses" in Simmons, J. S., and Gentzkow, C. J., Laboratory Methods of the United States Army, 5th ed., chapter 33, Lea and Febriger, Philadelphia, 1944.
16. PIERCE, M. E., KEMPF, J. E. AND SOULE, M. H.: *Proc. Soc. Exper. Biol. & Med.*, **48**: 604, 1941.
17. MUDD, S. AND ANDERSON, T. F.: *J. Am. M. Ass.*, **126**: 632, 1944.
18. HENLE, W. AND HENLE, G.: *Science*, **98**: 87, 1943.
19. ZIEGLER, J. E., LAVIN, G. I. AND HORSFALL, F. L. JR.: *J. Exper. Med.*, **79**: 379, 1944.
20. MILLER, G. L.: *J. Exper. Med.*, **79**: 173, 1944.
21. FINDLAY, G. M.: *J. Roy. Miscrop. Soc.*, **56**: 213, 1936.
22. JENSEN, J. H.: *Phytopath.*, **26**: 266, 1936.
23. *Idem*: *Phytopath.*, **27**: 69, 1937.
24. PRICE, W. C.: *Quart. Rev. Biol.*, **15**: 338, 1940.
25. CRAIGIE, J.: *Canad. Pub. Health J.*, **29**: 448, 1938.
26. BLISS, C. I.: *Ann. App. Biol.*, **26**: 585, 1939.
27. FISHER, J. W.: To be published.
28. Matheson Commission: Epidemic Encephalitis: Etiology, Epidemiology, Treatment, Third Report, Columbia University Press, pp. 11-16, New York, 1939.
29. LEVADITI, C., HARVIER, P. AND NICOLAU, S.: *Ann. Inst. Pasteur*, **36**: 63, 1922.

A sound mind in a sound body is a short but full description of a happy state in this world. He that has these two has little more to wish for and he that wants either of them will be but little better for anything else.—John Locke.

URINARY TRACT CALCULI*

H. Ostry, M.D.

Colonel Belcher Hospital, Calgary, Alta.

THE question is so frequently asked, "What is the cause of stone in the urinary tract?", that I thought it would be of interest to discuss some of the etiological factors in calculus formation. The subject is such a large one that one can only deal with certain aspects of the problem. Though many of the factors involved in stone formation are unknown the causes seem to be gradually approaching solution.

Some of the factors that have a bearing on the problem are diet, disturbances of metabolism, urinary tract stasis, infection, changes in the chemistry of the urine, geographic and climatic influences, age, race, and diathesis. To begin with let us consider the composition of urine as it relates to stone formation. Urine is a supersaturated solution of uric acid, phosphates and oxalates, of calcium, magnesium, etc. These are found in much higher concentration than they can be dissolved in water. They are kept in solution through the protective action of colloids. Under certain conditions there is a disturbance of this crystalloid-colloid equilibrium so that the dissolved crystalloids are precipitated.

There are six chemical types of urinary tract calculi. They often contain small quantities of other constituents to a varying degree. Calculi are not always pure, that is of only one chemical constituent, though they are usually composed of one main chemical substance.

1. *Calcium oxalate calculi.*—These are very hard. They form a large group and in some districts form a very high percentage of all stones. They usually occur in acid urine but also in an alkaline and neutral reaction. They are not caused by urinary tract infection. They usually do not attain a large size. In a series of 100 cases at the Royal Victoria Hospital in Montreal they formed 50% of the stones. From statistics by various authors it seems that they form more than 30% of calculi in the United States.

2. *Calcium carbonate stones.*—These are rarely found in pure form. Calcium carbonate is often a constituent of phosphatic calculi.

3. *Calcium phosphate,* and

* Read at Staff Meeting, Colonel Belcher Hospital, November 13, 1946.

4. *Magnesium ammonium phosphate.* (These can be grouped together. They usually occur in an alkaline urine but they may occur in acid urine).—Often they occur together and with calcium carbonate. They may form very large calculi. They often occur in presence of infection, particularly by urea-splitting organisms.

5. *Uric acid stones.*—These are rare in pure form, usually occurring as sodium, potassium or ammonium urates. They occur in strongly acid urine and this seems to be the most important factor in their formation. An excessive purine diet is more apt to cause their formation.

6. *Cystine stones.*—Cystine is an amino acid. Such stones occur only in those with cystinuria, that is, patients who secrete cystine in their urine. It is a derangement of cystine metabolism. Only a small percentage of such cases form stones. They occur only in an acid urine and usually without infection. Cystine stones can be prevented by appropriate diet and alkaline therapy. Some can be dissolved by the same measures. It is a familial condition.

7. *Xanthine stones.*—Xanthine is an amino acid. Such stones are uncommon. They arise from a derangement of purine metabolism leading to excessive excretion of xanthine.

Calcium stones form the majority of calculi. The calcium radicle seems to play the chief rôle, the acid radicle being only subsidiary. According to MacIntosh the presence of magnesium in a stone is of some importance. If present one should suspect urea-splitting bacteria as an important etiological factor.

Geographical Distribution of Stone

There are certain stone areas in the world where calculi occur with unusual frequency. Such regions occur in India and China. The people in these areas subsist on an improperly balanced diet. It is stated that calculi occur more frequently in southern California and southern Florida than in any other part of the United States. In England stone areas occur in Derbyshire, and Westmoreland. In Turkey, Gursel noted that calculi occurred in regions where the people lived on an inadequate diet. Stone areas have been noted in Egypt, Palestine the Valley of the Volga, in Russia, and in Dalmatia. In Kwangsi, calculi are frequent and this is the poorest province in China. The diet here consists mostly of boiled polished rice. Milk, fruit, meat and vegetables are not often eaten. In Syria at the American Presbyterian Hospital, bladder stones were often found (75% at the ages of 1 to 7 years). This was attributed to vitamin A deficiency. After the first World War calculus disease definitely increased in certain parts of Europe where the diet was poorly balanced over long periods of time. A most remarkable phenomenon was noted in the area of Central Europe blockaded during the World War I. Starting about 1919, reaching a sharp peak in 1924 and remaining sustained until 1937 there was a striking increase in calcium oxalate stone, at times reaching 10 times the usual incidence. Calcium oxalate stones were said to form 65 to 90% of all calculi. The stones were small, renal in origin, often unilateral, easily passed, and frequent in middle aged people. They recurred only infrequently.

In Finland and Switzerland calculi are rare. The people live on a diet very rich in vitamin A, drink much milk and eat many milk products. Vermooten noted that renal calculi are very infrequent in the South African negroes, based on the records of over a million admissions to the Johannesburg General Hospital. The negroes here live on a simple stable diet, rich in vitamin A, which has an acid-ash base, low in calcium. On the other hand the white population from the records of 126,000 admissions to hospital showed renal stone in the ratio of 1:460. In England and France during the last century calculus disease was much more frequent than at present and was common in childhood. At present calculus disease is rare in childhood in these countries. This is due to the modern progress in diet and nutrition. Davalos in Equador noted the rarity of stones in this region, which is a wet tropical country. He found only one stone in 60,000 patients.

Experimental Data in the Problem of Calculi

Renal and vesical calculi have been produced in animals on diets deficient in vitamin A. It has been shown that this deficiency causes a keratinization of the epithelium of the urinary tract. It is believed that the desquamated epithelial cells may act as a nucleus for stone formation. Vitamin A deficiency causes poor night vision as shown by the biophotometer test. Higgins in 1935 did a routine biophotometer test on a series of patients with calculus disease and 68% of these showed vitamin A deficiency.

Though marked deficiency does not occur in the United States, it seems that it may be more frequent in a milder form than is presumed. The biophotometer test should be routine in all stone cases.

Hammarstan in a most exacting experiment utilizing over 900 rats not only produced calculi but apparently illuminated some of the pathogenic factors involved. A magnesium-poor diet in rats produced calcium oxalate stones with or without an adequate intake of vitamin A and D. This is a relatively new concept that may possibly shed light on the previously mentioned stone wave in Central Europe after World War I. The magnesium content of food varies with the content of this element in the soil. A low magnesium, high oxalate, low vitamin diet, gave the highest incidence of stones in these rats. An analysis of the urine of the animals with calcium oxalate stone showed it to be acid in reaction and sterile. If the diet yielded a low urine pH, *i.e.*, acid in reaction, calcium oxalate stones were formed. With an increase in the pH to the alkaline side, calcium phosphate stones were formed.

Hammarstan also succeeded in decalcifying preformed calculi. Animals were kept on the stone producing diet until the x-rays revealed calculi. The diet was then changed to one rich in calcium, magnesium, and vitamins. After several months the animals were killed and showed a complete or almost complete dissolution of the stone but with the organic matrix still present.

Randall's initiating lesion or plaque.—In 1937 Randall after a series of researches presented what he considered one of the causes of renal stone. He studied the kidneys of some 609 cadavers of which some 140 revealed a lesion on the papillæ of the kidney which he calls the initiating lesion or "milk patch". It varies in size from the tiniest spot to 2 to 3 mm. in diameter. Microscopically these plaques show a deposit of calcium entirely devoid of inflammation. At first this calcium lies below the surface of the cells. Calcium continues to be deposited until it forms a definite plaque. This is followed by the loss of the covering cells. The plaque increases in size, breaks free, and leaves an eroded surface. A calculus is thus started on its way with further deposition of urinary salts. One must note that wherever there is cell death calcification follows. There is now a greater tendency to do a calycectomy in cases of renal stone where the involved stone containing calyx is eroded, injured or shows poor drainage. This is done with the view of preventing stone recurrence.

Infection of the urinary tract as an etiological factor in calculus formation.—Bugbee in a series of 29 cases of renal stones found definite history of pyelonephritis in 23 preceded the stone.

In 1925 the importance of urea-splitting bacterial infections was discovered as a very potent cause of stone formation. It is a very important factor in calculus recurrence. Many strains of bacteria have this property of splitting urea in the urine into ammonia and carbon dioxide, thus rendering the urine alkaline. Calcium salts are precipitated in an alkaline medium, so stones are easily formed. It is practically impossible to render urine acid in reaction in the presence of urea-splitting bacteria. A persistently alkaline urine usually means urea-splitting bacteria and is fraught with danger. It is very difficult to eradicate such a type of infection. Shute and Suby state that in their experience urea-splitting organisms are the chief single cause of calculi, in 54% of their cases. The stone recurrence rate is given variously as 4.5 to 54% by various authors. In some medical centres the stone recurrence rate has been considerably reduced by the newer knowledge of some of the etiological factors.

In 1921 Rosenow and Meiser showed the specificity of certain strains of streptococcus in the formation of urinary calculi. They inoculated the pulp of the teeth of six dogs with streptococcus isolated from the urine of patients with urinary stones. Calculi developed and streptococci were isolated from the urine of the animals.

In connection with foci of infection as a cause of urinary tract infection and maintaining it, it is interesting to note that Everett, Scott and Steptoe report treating a series of 41 cases of urinary tract infection, the majority *B. coli.* These had proved refractory to ordinary methods of treatment. They used sulfasuxadine with the object of affecting the flora of the intestinal tract which acted as a massive reservoir continually infecting the urinary tract. In 91% of the cases the urine was rendered sterile by this treatment.

Obstructions in the urinary tract and urostasis as factors in calculus formation.—With

obstruction in any part of the urinary tract, stasis of urine occurs. With stasis one is very apt to get infection and with infection a tendency to stone formation. The most frequently encountered renal lesion is hydronephrosis and the etiological cause may be varied. It may be congenital, mechanical, neurogenic, etc. The incidence of obstructive factors in stone cases is quite high and in treatment one must rectify these obstructive factors to prevent stone recurrence. Obstructions even in the lowest part of the urinary tract may play a part. Thus Dourmashkin and Solomon in a series of 84 cases of old urethral stricture found renal calculi in 22.6%. Pus and blood in the urine is so common in urethral stricture that their significance in the diagnosis of kidney or ureteral stones may be overlooked.

The rôle of recumbency and immobilization.—This factor especially over a prolonged period of time such as occurs in fractures and spinal cord injuries has come very much to the fore in war casualties. The opportunity for observing large numbers of such cases was available in this war. An increased calcium excretion in the urine has been shown to play an important rôle in calcium stone formation. During recumbency over a long period of time there is decalcification of the immobilized bones and a great increase in urinary calcium. This persists for the first two months and then gradually returns to normal, even though recumbency is continued. These first two months are the periods of danger when small calcium precipitates may accumulate to initiate a stone. However these minute stones may not manifest themselves for months or even years later, in the meantime increasing in size. Some of these may become evident early. Most of them may pass without symptoms or with symptoms, leaving one or two to remain behind and grow. In the presence of a urinary tract infection they may grow very rapidly in size; in one proved case as early as 18 days.

The point that must be stressed is that such small early stones may be perfectly symptomless, becoming evident only months or years later. Then, most patients drink insufficient fluids which results in a more concentrated urine and a greater tendency to calcium precipitation. An individual lying flat on his back is in a more vulnerable position for stasis to occur. In such a position the kidneys are below the level of the ureters and bladder, so that there may be a continuous pool of urine in the renal pelves and calyces adding their share to the possibility of calcium precipitation. Should a focus of infection be present in the tonsils, bowel, or an osteomyelitis, one can see that the urinary tract may become infected.

Conditions in which stone occurred (Flocks).—In 277 fractures of the spine 5% developed renal or vesical calculi. In 101 fractures of the pelvis 7% developed renal or vesical calculi. In 83 strictures of the urethra 16% developed renal or vesical calculi.

PROPHYLACTIC TREATMENT AGAINST STONE FORMATION IN BED-FAST PATIENTS

1. *Force fluids.*—2,500 to 3,000 c.c. fluids, preferably more, in 24 hours. This dilutes the urine and helps wash out any urinary sediment.

2. *Diet.*—A neutral ash diet, low in calcium, large doses of vitamin A. When out of bed and if calcium excretion in the urine is decreased, change to acid ash diet.

3. *Control of stasis.*—It is important that patients frequently change position in bed and carry out a routine regimen of exercises, of uninvolved parts of the body, when this is feasible.

4. *Urinalysis.*—To be done frequently to check for white and red blood cells and bacteria.

5. *Control of infection.*—Sulfacetamide is the most soluble of the sulfonamides and is best for most purposes.

6. *Continue the above* therapy at least three months after the patient is out of bed especially those who have been bed-fast a long time. In these, a K.U.B. x-ray every 1 to 3 months is indicated. Some will require periodic check-up as long as 1 to 2 years. The importance of continuation of therapy for at least 3 months after recumbency has ceased and check up x-rays at frequent intervals is not generally recognized.

THE RÔLE OF HYPERPARATHYROIDISM IN CALCULUS FORMATION

Hyperparathyroidism, osteitis fibrosa cystica, or von Recklinghausen's disease is due to an adenoma or to hyperplasia of the parathyroid glands. The full-blown disease is characterized by bone cysts, formation of giant cell tumours, weakness, hypotonia, anorexia, polyuria, and pain in the bones. The blood calcium is elevated and the phosphorus lowered. Surgical removal

of hyperplastic parathyroid tissue or the adenoma usually cures the disease. Renal stone often occurs in this condition. It is considered a rare disease. However, it seems that hyperparathyroidism, in a milder form exists, with fewer and milder symptoms.

There has been a revival of interest in the condition of hyperparathyroidism in recent years, due to the work of Allbright, and his associates at the Massachusetts General Hospital. They pointed out that hyperparathyroidism can occur with bone disease without renal lesions or calculi. It can occur with renal lesions, without bone involvement. Therefore neither bone lesions nor renal lesions are necessarily conspicuous. They showed that involvement of the urinary tract is a common and more important manifestations of the disease and it is an etiologic factor in causing renal stone in an appreciable number of cases. Cope states that 10 to 15% of patients with renal stone investigated by himself or by Allbright are eventually proved to have hyperparathyroidism as the cause. The disease has been missed in the past. The diagnosis was made infrequently at the Mayo Clinic. The first observed case was in 1929, and between 1929 and 1942 only 14 cases were found. Early in 1943 a deliberate attempt was made to improve diagnostic accuracy and the collaboration of internists, surgeons, and urologists was obtained. In only 2½ years 24 additional cases have been proved at operation at the Mayo Clinic.

Every patient having a calcium stone should be suspected of hyperparathyroidism. At present the diagnostic criteria of hyperparathyroidism are 3 in number: (1) an elevated serum calcium, not necessarily much above normal; (2) a reduction of serum phosphorus; (3) an increased excretion of calcium in the urine. A low level of urinary calcium excretion usually rules out hyperparathyroidism.

The early symptoms of hyperparathyroidism are notoriously vague, and seldom pathognomonic, so that to make a diagnosis a special deliberate search must be made. In many cases the calcium phosphorus changes in the blood are minimal and their significance cannot be evaluated without repeated examination. The patient must be observed over a long period of time. In about 10% of all renal calculi, recurrence eventually develops after operation. The rôle of hyperparathyroidism may prove to be a factor of much importance in this group.

Follow up Care After Calculus Removal

It is obvious then from what has been said that many etiological factors are involved in calculus formation. One must have a knowledge of all these to treat and prevent stone formation. Some stones can be prevented but despite all efforts others continue to recur.

It is very important to analyze all stones removed. Unfortunately, once a stone is removed the patient promptly proceeds to forget about it, as too often the doctor also does. Frequent follow-up of the patient should be continued postoperatively for a long time, particularly in some types of stone. The diabetic has been educated to frequent check-ups of his condition. So too, should the calculus patient, though perhaps not to the same degree. The rate of renal stone recurrence has been stated as 4.9 to 56% by various authors. In any event it is of sufficient frequency to warrant more attention. Certain measures can be taken to prevent recurrence in many cases. The diabetic has frequent urine examinations. So too should the calculus patients be watched for pyuria, hæmaturia, bacteruria, etc., and the acidity of the urine checked. A K.U.B. x-ray of the urinary tract can easily be taken at intervals as called for. Urinary calcium excretion can be estimated. The diet can be regulated according to the type of stone. Sufficient vitamins, particularly vitamin A should be included in the diet. A sufficient quantity of fluid should be taken.

All of this of course, is the ideal, but is rarely carried out in practice.

Bibliography

1. McCarrison, R.: *Brit. M. J.*, 1: 1009, 1931.
2. Holmes, J. and Coplan, M. M.: *J. Urol.*, 23: 472, 1930.
3. Brown, R. K. and Brown, E. C.: *Surgery*, 9: 415, 1941.
4. Flocks, R. H.: *J. Urol.*, 44: 183, 1940.
5. *Idem*: *J. Urol.*, 43: 214, 1940.
6. Keyser, L. D.: *J. Urol.*, 50: 169, 1943.
7. Barney, J. D. and Mintz, E. R.: *J. Urol.*, 36: 159, 1936.
8. Higgins, C. C.: *J. Urol.*, 40: 184, 1938.
9. Kearns, W. M.: *J. Urol.*, 43: 598, 1940.
10. Melvin, P. D. and Andrews, J .C.: *J. Urol.*, 37: 655, 1937.
11. de la Pena, A. and E.: *J. Urol.*, 52: 108, 1944.
12. Hamer, H. G. and Mertz, H. O.: *J. Urol.*, 52: 475, 1944.
13. Barney, J. D. and Jones, G. E.: *J. Urol.*, 45: 1, 1941.
14. Boyd, M. L.: *J. Urol.*, 45: 647, 1941.
15. Flocks, R. H.: *Clinics*, 3: 103, 1944.
16. *Idem*: *J. Am. M. Ass.*, 130: 913, 1946.
17. Keating, F. R. and Cook, E. N.: *Proc. Staff Meet. Mayo Clin.*, 19: 159, 1944.
18. Black, B. M. and Sprague, R. G.: *Proc. Staff Meet. Mayo Clin.*, 22: 73, 1947.
19. Kowallis, G. F.: *Proc. Staff Meet. Mayo Clin.*, 16: 129, 1941.
20. Keating, F. R. and Cook, E. N.: *J. Am. M. Ass.*, 129: 994, 1945.
21. Rogers, H. M.: *J. Am. M. Ass.*, 130: 22, 1946.
22. Cawker, C. A.: *Canad. M. A. J.*, 55: 19, 1946.
23. Jeghers, H. and Murphy, R.: *New England J. Med.*, 233: 208, 238, 1945.
24. Suby, H. I.: *Proc. Roy. Soc. Med.*, 37: 609, 1944.
25. Dodson, A. I. and Clark, J. R.: *J. Am. M. Ass.*, 132: 1063, 1946.
26. McIntosh, J. F.: *J. Clin. Invest.*, 21: 751, 1942.
27. Patch, F. S.: *Canad. M. A. J.*, 31: 250, 1934.

PHRENIC NERVE INTERRUPTION—TECHNIQUE AND INDICATIONS*

G. A. P. Hurley, M.B.

Montreal, Que.

AMONG the collapse therapy procedures for the treatment of pulmonary tuberculosis, paralysis of the hemidiaphragm still holds a valuable place. It is perhaps the least incommoding of the operative measures for this disease that are in use today, and given the proper indications is often effective in securing arrest. The recent revival of pneumoperitoneum and its undoubted efficacy, particularly when used in conjunction with phrenic interruption has served to arouse fresh interest in the latter operation. Except in rare instances, temporary rather than permanent interruption of the phrenic nerve is done for the following reasons:

1. It is well, if possible, to leave the patient with a functioning diaphragm at the termination of treatment so as not to permanently impair the respiratory function. This is important in tuberculosis of the lungs because extension of the disease to other portions of the lungs may necessitate further collapse therapy, and the extent of this that can be wisely undertaken depends on the available lung function.

2. Permanent paralysis of the diaphragm has on occasion led to undesirable complications such as atelectasis or gastro-intestinal disturbances. It is also possible that a non-functioning diaphragm may interfere with the circulatory function in hindering the venous return. This is probably of no consequence in youth but may lead to undesirable results with advancing years.

The commonest indications for permanent interruption of the phrenic nerve at present are: (1) To occlude an empyema cavity in association with thoracoplasty. (2) To collapse a lung that is totally diseased in conjunction with thoracoplasty. (3) To secure permanent arrest of a lower lung lesion which after three or four periods of temporary paralysis shows signs of reactivation, although control had been secured while the diaphragm was paralyzed.

The chief indications for phrenic interruption in pulmonary tuberculosis may be briefly classified as follows:

1. *The independent phrenic.*—Phrenic interruption used as an independent measure, or possibly reinforced by pneumoperitoneum. This refers to (*a*) cases of lower or mid-lung disease; (*b*) cases with minimal or rarely, moderately advanced disease of the upper lung for which active treatment is indicated and in which pneumothorax or thoracoplasty are inapplicable.

2. *The auxiliary phrenic.*—Phrenic interruption used in conjunction with some other collapse measure. Here are included cases of disease of any part or parts of the lung that are also being treated by artificial pneumothorax or thoracoplasty, but in which these latter procedures are not entirely effective in controlling the disease. Among these one lists thoracoplasty patients who in addition to disease of the upper and mid lung show involvement of the lower zone—a part of the lung which is not readily collapsed by thoracoplasty. Rarely, a patient with an established pneumothorax in which some or all of the adhesions have been divided without securing arrest, and in whom there is some contraindication to thoracoplasty may come under this category.

3. *The preparatory phrenic.*—Phrenic interruption used preparatory to some other collapse measure. This indication is practised less today than formerly. In the past it has been used typically in a case of acute disease where one is reluctant to induce pneumothorax owing to the fear of pleural effusion and empyema, or where one regards the course as too acute to permit a safe thoracoplasty. The theory underlying this use is that paralysis of the diaphragm may give sufficient immobilization of the lung so that the acute process may subside and later either pneumothorax or thoracoplasty may become feasible propositions. While the theory sounds plausible and has been found to work on occasions, it is generally desirable to secure collapse of the upper portion of the lung if this is the part involved, as soon as possible. Too often it is found that paralysis of the diaphragm may not influence the course of the disease in the upper lung, while it may tie one's hands in contemplating collapse by thoracoplasty. This is so because experience has shown that those cases with paralyzed diaphragms are very liable to develop atelectasis after thoracoplasty, apart from the fact that the reduced lung function by reason of the phrenic interruption may contraindicate thoracoplasty from the first.

* From the Grace Dart Hospital, Montreal.

THE TECHNIQUE OF PHRENIC NERVE INTERRUPTION

The procedure is unique in that the same operation is repeated twice or oftener. Clearly the finding of the nerve becomes more difficult with succeeding operations in that the normal landmarks are displaced or obscured by scar tissue. For this reason it is well that particular attention be paid to the technique of the first operation so as to make the succeeding ones as easy as possible. It is my belief that if certain precautions are taken repeated interruptions become much easier. The following is the mode of procedure suggested for the first operation:

Through a short incision in the supraclavicular area extending for two to three inches posteriorly from the sternal head of the sterno-mastoid muscle one-half inch above and parallel to the clavicle, the posterior triangle of the neck is opened into. The superficial fascia is divided in the line of the incision and the deep fascia is exposed. The external jugular vein is best divided between ligatures particularly if it lies in fairly close proximity to the sterno-mastoid. This will obviate its division at a repeat operation when it will be more difficult to define. The deep fascia may be divided by blunt dissection and the supraclavicular fat pad exposed. The fat pad is separated with the scissors and the anterior scalene muscle defined with, among other things, the phrenic nerve, the transverse cervical, and suprascapular arteries lying on it. It is a good practice to remove all or at least the greater part of the fat pad so that it will not become involved in scar tissue together with the two arteries named. Dissection through this mass at a later operation may prove difficult and dangerous in that the arteries may be inadvertently divided and cause serious hæmorrhage. For this reason it is well at the first operation to divide these arteries between ligatures. This leaves the phrenic nerve uncovered by any structures other than the skin the omohyoid muscle and a layer of scar tissue. The latter tissue can be freely dissected now since one knows that it cannot contain the aforementioned blood vessels and no vulnerable structures intervene between the skin and the phrenic nerve in the line of the approach.

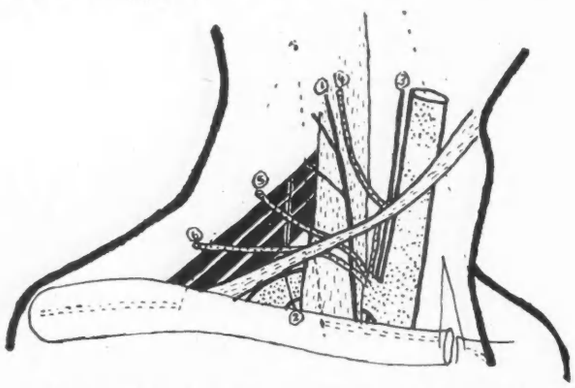


Fig. 1.—(1) Phrenic nerve; (2) accessory phrenic nerve; (3) vagus nerve; (4) ascending cervical artery, branch of the inferior thyroid artery; (5) transverse cervical artery; (6) suprascapular artery. The brachial plexus is shown in black, the common carotid and subclavian arteries stippled, and the omohyoid and anterior scalene muscles striated. The trapezius and sternocleidomastoid muscles and the clavicle are shown in outline. The veins are not shown.

As soon as the nerve is exposed its identity is proved by twitching it gently with an artery forceps when an epigastric thrust of variable force will be produced due to the resulting diaphragmatic contraction. A small quantity of novocain 1% is next injected under the perineurium, and the nerve is left for the moment. An essential part of the operation has to do with the finding and resection of a possible accessory phrenic nerve. This structure is looked for in the angle between the brachial plexus and the main phrenic trunk. It usually comes off from the fifth cervical nerve but may be included in the nerve to the subclavius muscle which usually springs from the point of junction of cervical nerves V and VI (Erb's point) where they unite to form the upper trunk of the brachial plexus. The accessory nerve is usually quite tenuous and difficult to identify and in order to ensure its resection it is well to clear away all the areolar and fatty tissue together with the prevertebral fascia in the angle between the brachial plexus and the main phrenic nerve trunk. Occasionally the accessory phrenic nerve is quite large and its identity can also be proved by means of the epigastric thrust.

Having dealt with the accessory phrenic nerve, the anæsthetized main trunk is crushed three or four times at the same spot with an artery forceps. The wound is closed in two layers with interrupted sutures of fine white cotton. The skin sutures are removed on the fifth postoperative day.

The patient is brought before the fluoroscopic screen on the day of the operation or the succeeding day. The paralyzed diaphragm is either immobile or moved passively by the action of the unparalyzed side. The most satisfactory test for paralysis of the hemidiaphragm is the sniff test. The patient inspires forcibly and shortly through the nose whereupon the active hemidiaphragm descends and the paralyzed side ascends. This phenomenon is known as the paradoxical movement of the paralyzed hemidiaphragm.

Ordinarily the duration of paralysis of the hemidiaphragm is about six months but it may vary between four and eight months. Refrigeration of a centimetre's length of the nerve (for example by ethyl chloride spray or carbon dioxide snow) in addition to crushing, will give up to ten months' paralysis of the diaphragm.

5458 Lavoie St.

A great man having been asked why he wore his sealring on his left hand, whereas the right possesses so much excellence, replied: "Knowest thou not that the meritorious are always neglected?"—The Sheik Sa'di of Shiraz.

PROTRUDED INTERVERTEBRAL DISC

H. H. Hepburn, M.D., F.R.C.S.[Edin.&C.]

Edmonton, Alta.

SO much has been said and written during the past few years about pain and the rôle of the pathological intervertebral disc, that historical review seems unnecessary. I shall simply add some personal observations and experiences. I should like to make two general statements. The first; that not all persons with low back or sciatic pain have a grossly diseased intervertebral disc; and the second; that not all persons with a pathological disc require surgical treatment. It is no doubt true that some of the cases given one of several possible diagnoses in the past, actually had pathological discs, but we must still recognize that there are other causes of low back pain.

I have been asked whether this disability is becoming more frequent, or simply more frequently recognized. I believe it is both. In addition, social and industrial evolution has made it increasingly difficult for a handicapped man to make a living, and for the average family to maintain a cripple. For these reasons his disability becomes more conspicuous, and application for relief more frequent. Assuming that the disability is actually on the increase one might suggest certain reasons. The old saying that many hands make labour light has no place in modern industry. The speeding up of labour and other efforts to cut production costs may be responsible for many back strains and injuries. The speed and violence of modern transportation vehicles contribute materially to back injuries. Declining physical fitness and increasing recklessness must be included. In female patients, changing fashions in dress, and increasing participation in various forms of physical exertion may be expected to increase the incidence of low back strain.

Coming more specifically to the pathological condition in the intervertebral disc, I would like to record another general observation. I think it is extremely rare, if indeed ever, possible, that protrusion, or extrusion, of any portion of a healthy intervertebral disc occurs immediately following any one acute strain or accidental injury. This introduces the difficult problem of assessing eligibility for compensation. Of course we recognize that an entire disc is never dislocated unless accompanied by the body of the vertebra to which it remains attached. What commonly happens is the protrusion of a portion of the nucleus pulposus or central core of the disc. I doubt if it is possible to extrude an entire, healthy nucleus pulposus, as one would express the pulp from the skin of a grape. What we commonly find is protrusion of a portion of a disorganized nucleus. If the posterior common ligament be ruptured, the protrusion becomes an extrusion in many cases. Why then does a nucleus become disorganized prior to the protrusion? Possibly as a result of one violent, accidental injury, or by repeated strains of lesser violence, accidental, or incidental to heavy labour. Possibly as a result of nontraumatic biochemical or pathological changes. Possibly it is a natural process of advancing age, similar to the loss of hair or teeth, or the atrophic changes in and about joints. The final strain that breaks the back of a camel, or of a man, may be a trivial one. Which then, in the problem of compensation, is the indictable incident; the malnutrition of the depression years, or the ravages of time, the initial strain when thrown from a motor cycle ten years ago, the repeated strains of shovelling coal for five years, or the slip when lifting a log yesterday? Which, if any, of three or four industries is to be charged with compensation? There does not appear to be any accurate answer to the question, but there does appear to be a solution of the problem in a system of national health insurance.

I shall not attempt to enumerate all of the symptoms and signs and laboratory aids by which one may arrive at the correct diagnosis. Volumes have been written during the past ten years on this subject and are available to those interested. Briefly, the symptoms are pain and impairment of function, common of course to other causes of disability. The distinctive signs are; spasm, loss of tone, volume and power in the muscles innervated by the affected nerve roots; alterations in sensation, hyperæsthesia or hypæsthesia; corresponding alterations in reflexes, depending in distribution upon the particular nerve roots involved. The correct interpretation of these phenomena requires accurate knowledge of anatomy and physiology, and some psychology. Laboratory aids include complete study of blood and urine, accurate and repeated temperature recordings, sedimentation tests, tuberculin tests, spinal

fluid examinations, and x-rays. Of the special x-ray procedures airograms are, in my experience, of little value. Lipiodol has objections. Pantopaque myelograms are of very decided value, but should be the last step, not the first. They are not necessary in all cases, and are not absolutely conclusive evidence under all circumstances.

I have intimated that not every patient with a protruded intervertebral disc requires surgical treatment. What then are the indications for surgical treatment; and what are the alternate procedures? Standards may vary somewhat with different neurologists and surgeons. My scale includes four items, as follows: (1) disabling pain; (2) sensory changes; (3) reflex changes, and (4) atrophy, or loss of tone in the involved muscles. At least three of these items must be present, and one of them must be disabling pain. If a case does not meet these requirements, I believe it should be treated by palliative, non-surgical measures, which include restriction of effort, possibly a change of occupation.

The first episode and many subsequent episodes will respond to rest. When the so-called first episode does not respond to rest I believe careful enquiry will show that it is not really the first episode. When I say rest, I mean absolute rest, flat in a sagless bed on a firm mattress. One pillow is allowed under the head and one under the knees. When the patient turns on his side, the pillow is placed between the knees and when on his face it is placed under his ankles. He may also require a thin pillow under the abdomen when there is much loss of lumbar curve. The patient is not permitted to sit up, even for meals. If carefully placed on a Gatz frame or folding bed, so that flexion occurs only at the hip joints, the head of the bed may be elevated at meal time by an attendant, and lowered immediately thereafter, to prevent slumping with flexion of the lumbar spine. When the patient turns over he must be rolled like a log. He is cautioned never to twist the shoulders or the pelvis separately. Of course he is never permitted up to the bath room. Great care must be exercised in putting such a patient on and off a bed pan. When available, a mattress with a narrow, removable section is an advantage. I do not use the Bradford frame because I am not able to make the patient comfortable on it. One must make him reasonably comfortable to secure his co-operation.

I like to have four or five such patients in a small ward. The routine is carried on for the first week after operation, when surgery is required. They soon develop a sort of school boy discipline. The stronger characters bolster up the weaker ones. When the morale in the ward deteriorates, as it sometimes will, I move out the ones that are spoiling the brew. I insist on strict attention to detail because I have seen so many cases where this routine has given results in two or three weeks, where less rigid routines for many weeks have failed.

During a rest treatment I do not employ any thermal or physiotherapy measures that necessitate the removal of the patient from his bed. Heat, in any form that can be employed in bed is a most excellent agent for the relief of pain and muscle spasm. I prefer an electric pad to the lumbar region. All of my patients are put on an alkaline salicylate mixture. I sometimes add a little iodine to appease my orthopædic colleagues. When a patient is restless or impatient a grain of phenobarbital is given three or four times in twenty-four hours, especially during the first week. When pain is severe, codeine or demerol, or dilaudid is permitted for a few nights. A compound aspirin tablet will usually suffice during daytime. I avoid these drugs if possible on account of the constipating effect, but the patient must be kept comfortable until he sees that he is getting results, which will usually be inside of a week.

If three weeks of this treatment does not give relief, or if disabling pain recurs when he is allowed up and repeated examinations confirm the correctness of the diagnosis, surgical treatment should be instituted without further delay, before the patient becomes a psychic as well as a physical invalid. Of course there is the occasional case where for economic or other reasons, the patient does not choose to accept a period of two or three weeks of enforced idleness, with the risk of subsequent recurrence, and may elect to have the immediate surgical relief. I think two weeks should be the minimum and three weeks the maximum period of rest treatment of this type. An additional three weeks of less rigid rest may be advisable in some cases.

The above routine of course does not apply in detail to the management of protrusions in the cervical region, which are comparatively

infrequent, and require special consideration. Of course there are some psychological problem cases, especially where compensation is involved, that may make it advisable to withhold surgical treatment, even when the surgical criteria are otherwise fulfilled. The morale and mental attitude of each risk must be evaluated, even then some errors in judgment may be made.

Possibly I should say a few words about some of the other non-surgical procedures. Steam baths or hot water baths or diathermy are helpful when the blood count and sedimentation tests indicate the presence of an element of low grade fibrositis. Local injections of procaine solution, or epidural sacral injections of normal saline solution may have some value in some cases, especially when the diagnosis is in doubt. I have abandoned epidural injections but still use an oxygen neurolysis, supplemented by sciatic stretching under pentothal anæsthesia for cases of chronic sciatica, without convincing evidence of protruded disc. I do not manipulate the back under general anæsthesia. Manipulation under anæsthesia may give relief in cases of chronic fibrositis, or may establish the diagnosis and make indications for surgery clear when a protruded disc is present. Less vigorous manipulations without anæsthesia undoubtedly give temporary relief in many cases. Prolonged traction has its advocates. I am not convinced of its merits. Prolonged immobilization is indicated where there are reasonable grounds for suspecting tuberculosis.

When surgical treatment has been decided upon there may be some differences of opinion about the best procedure to be followed. The opinions about to be recorded are those of the author. To fuse or not to fuse is the main question. I am a neurosurgeon. Generally I do not do fusions of the spine but I recognize that some patients suffering from low back pain may require such an operation. When pain is due to an unstable vertebra resulting from a congenital defect in ossification, or from a fracture, some type of fusion would appear to be indicated. Even if the patient has a mild degree of protrusion of an intervertebral disc, such an operation may give complete relief, especially if there is no nerve root fixed by adhesions. When there is a gross protrusion with adhesions of a nerve root sheath, and especially when a rupture of the posterior common ligament with extrusion of a loose fragment of nucleus pulposus has already taken place a fusion cannot be expected to give complete relief. I have recently removed a large extruded fragment of a nucleus from a patient who had previously had a spinal fusion with persisting pain. The extrusion was confirmed by pantopaque myelograms. Neither the myelography nor the subsequent operation presented the difficulties I had anticipated. If these arguments are sound it would appear advisable that the suspected disc should be examined before a fusion is done in any case where a protrusion is suspected. I frequently do this in collaboration with an orthopædic surgeon when he proposes to do a fusion. I emphatically do not believe that fusion should be performed as a routine in cases where a protruded nucleus has been removed, uncomplicated by any developmental defect. Experience has shown fusion to be unnecessary in the great majority of cases. If it has to be done later in a few cases this does not constitute a calamity.

The modern operation for removal of a protruded nucleus is by an interlaminar approach through a window in the ligamentum flavum. In probably half the cases it will be found necessary to remove a portion of one lamina, in order to obtain adequate decompression and exposure, to avoid injury to a nerve root. Thorough curetting of the degenerated disc is accepted practice, to prevent subsequent extrusion of additional fragments.

A problem in judgment is presented when the operative findings are not in keeping with the clinical picture. There are those who would close the wound and change the diagnosis. Others would proceed to incise and curette the disc. If the disc is unduly bulging and boggy it undoubtedly should be curetted. It may be necessary to manipulate the table to varying postures before this decision can be made. An exploratory incision into a disc should not be made until one is reasonably certain that curetting must follow.

I do these operations under spinal anæsthesia and make a practice of showing the patient what I have removed and assuring him that his back has not been weakened by the operation.

In cases where postoperative oozing may be anticipated, it is advisable to place a Penrose drain down to the dura for twenty-four hours. This may avoid embarrassing postoperative pain, or foot-drop. Great care should be ob-

served in liberating and retracting the nerve root, for the same reasons.

The postoperative patient is kept flat in bed for seven to ten days, then permitted up, but instructed not to bend except from the hip joints until three weeks from the date of operation. During the second three weeks he gradually increases the range of all movements. At the end of six weeks from the date of operation he should have attained his full range, and be fit for light work. If he is an office man, or not on compensation, he will probably be back on his job before six weeks. If he is a labouring man it is advisable that he take another four weeks to recondition himself. At the end of ten weeks the average man should be fit to resume industrial employment, but he is warned to watch his step and avoid unusual twists and sudden strains for at least a year. He is shown how to use muscles of his limbs rather than those of his back in lifting. If a man has previously been engaged in very heavy labour, this may necessitate some restriction or even a change in occupation.

I never promise a complete cure. I tell a man he may get 100%, and many do, but I expect him to be able to do from 75 to 90% of what he could do during the previous five years, and do it in comfort, provided he uses good judgment. I think it is important to avoid discouragement and to prevent recklessness that might result from undue optimism.

RADICAL PERINEAL PROSTATECTOMY FOR CARCINOMA OF THE PROSTATE*

C. Agnew Cawker, B.A., M.D.

Vancouver, B.C.

THE history of perineal prostatectomy is the saga of the late Dr. Hugh Hampton Young, of the James Buchanan Brady Urological Institute, Johns Hopkins Hospital, Baltimore. It was in 1902 that Dr. Young designed his prostatic tractor and performed his first perineal prostatectomy with it, enucleating the lateral and median lobes. It was in studying specimens removed by the enucleating perineal prostatectomy that he discovered three cases in which small areas of cancer were present and realized that by radical removal of the prostate with its capsule and seminal vesicles a permanent cure might easily have been effected.

A further study of autopsy specimens of cancer of the prostate confirmed his opinion as to how this growth spreads and the possibility of radical cure.

Carcinoma of the prostate spreads by invasion along planes of least resistance, by the lymphatics to pelvic and lumbar nodes and may even go on to involve the inguinal, thoracic and supraclavicular nodes and such organs as liver, lungs and pleura, although these are usually of late occurrence. Most commonly it spreads by the blood stream. Metastases are found most commonly in the bones of the pelvis, spine and femur. Boyd says these must be attributed mainly to the blood stream. There is an abundant nerve supply in and around the prostate and the perineural lymphatics may be involved relatively early with later lymphatic spread by permeation and embolism.

The lymphatic spread also serves to explain the very frequent involvement of the bony pelvis and lumbar spine. Pain is an indication of perineural involvement. The periprostatic tissue and particularly the rectum are protected by the two layers of Denonvilliers' fascia until late. Cancer, beginning in the posterior lobes and then invading the lateral lobes, usually involves the tissue beneath the trigone, around the seminal vesicles and vasa without passing into the urethral or vesical lumen. In some cases it breaks into the lumina of the ejaculatory ducts and from there into the lumina of the seminal vesicles and the ampullæ. The mucous membrane of the prostatic urethra and bladder are rarely invaded except late in the disease. The tumour may ultimately break into the bladder and form an ulcerative growth. This is more apt to happen after transurethral and enucleating prostatectomies. The membranous urethra is remarkably free from invasion. In two of Young's cases the growth had travelled along the urethra to invade the bulbous portion. It also has been reported as invading the corpora cavernosa causing priapism. The peritoneum may be invaded by direct extension from the prostate without involvement of either bladder mucosa or seminal vesicles.

On April 7, 1904, the first of Young's epoch-making radical perineal prostatectomies was done under ether anæsthesia, using the inverted "V" incision. Other operators have been credited with the first radical operations for carcinoma of the prostate. Billroth in 1867 reported two cases done through a median perineal incision, one in a lad of age 20. Recurrence was present in two months and the patient died one year later. The other patient died of peritonitis four days after the operation. Excision of the prostate without the seminal vesicles was carried out by Leisrink in 1882, Czerny in 1889, and Fuller in 1898. Leisrink used the curved perineal incision of Celsus. Zuckerkandl in 1889 further developed the approach by painstaking dissection of the perineum. It was the "dissecting operation" of Leisrink and Zuckerkandl that Dr. Young so ably perfected.

* From the Department of Urology, Shaughnessy Hospital, Vancouver, B.C.

Read at the monthly staff meeting Shaughnessy Hospital, January 14, 1947.

Küster in 1891, through a suprapubic incision, enucleated the entire bladder and through a perineal incision divided the membranous urethra, separated the prostate and the seminal vesicles from the surrounding structures, divided the ureters just above the bladder, removed the bladder, vesicles, and prostate in one piece and transplanted the ureters into the rectum. However, the patient died five days later. Proust and Albarran of Paris, in 1901 devised a perineal prostatic tractor, described the median capsular incision, individual lobar enucleation and developed a perineal "frame" or table. Harris in 1902, through a suprapubic incision, carried out transverse division of the urethra in front of the prostate, removing the entire prostate and all but the vertex of the bladder and then transplanted the ureters into the remaining portion of the bladder. No attempt was made to suture the bladder to the membranous urethra. The patient died two months later.

Dr. Hugh Young did his first perineal prostatectomy in 1898 while still resident at Johns Hopkins Hospital under Dr. Halsted. A suprapubic cystotomy was done first, then a perineal section, the prostate being pushed down to the perineum by an assistant's hand in the suprapubic wound. The prostate was exposed through a median and lateral perineal incision on the right side. Dr. Young stated that this patient soon had a recurrence of his cancer and died nineteen months later. The experience of this case showed conclusively that earlier diagnosis and more radical operation would be required to cure these cases of carcinoma.

It was as the guest speaker at the Wisconsin Medical Society meeting at La Crosse in June, 1905, that Dr. Young first described his radical operation. He analyzed 40 cases of carcinoma of the prostate and made a plea for routine rectal examination of all male patients and that all hard nodules in the prostate be treated as malignant and a biopsy done.

There have been quite a number of modifications of the original Young technique. In 1912 Gayet modified it, without advantage according to Young. Voelecker's modification was somewhat similar. Pauchet did a suprapubic extracapsular removal of the prostate and seminal vesicles. He stated that this operation occasioned a good deal of bleeding and he advised tight packing and suturing of the cavity. In 1922 Geraghty proposed a modification of Young's radical operation which Young stated made it only a subtotal operation and usually afforded poor results. In 1928 T. E. Gibson of San Francisco, while using Young's technique, emphasized the importance of eliminating packing and bags to control hæmorrhage and suggested the use of a retained urethral catheter and complete closure by suture. In 1940, Lowsley presented another modification which applied only to closure. Lowsley uses ribbon catgut to approximate the wide open vesical neck to the membranous urethra. In 1942, Elmer Belt presented 50 cases operated on over a twenty-year period with 58% cure. This operation varies in the approach to the prostatic apex and method of anastomosis of vesical neck and membranous urethra.

Dr. George Gilbert Smith of the Massachusetts General Hospital, in 1929, printed a review of 23 cases followed for six years. Fifteen were still living and most of them showed no evidence of recurrence. In 1941 he reviewed 71 cases of radical perineal prostatectomy. Of the cases of cancer of the prostate seen by this group 20% were considered suitable for total prostatectomy. Thirty-five of the 71 patients died of recurrence, 21 had had five years or more since operation and 20 patients examined one to twelve years postoperatively were free from evidence of recurrence.

In 1940 Dr. Colston presented a study of 91 cases from Johns Hospkins Hospital, in 38 of whom the preoperative diagnosis was favourable: 50% had lived five or more years postoperatively. He states: "All clinicians—medical, surgical, and urological—should therefore be stimulated to recognize this disease in its early stages while hope of complete removal is still present". In 1944 after an intense study of the ultimate result of cases of Young's radical perineal prostatectomy at Johns Hopkins Hospital Dr. Colston found that nearly 50% were free from recurrence or metastasis from 5 to 27 years postoperatively. Approximately 21% of their cases of carcinoma of the prostate were first seen early enough for radical operation.

Dr. Alexander Randall stated in 1941:

> "When we realize that the radical operation cuts across the membranous urethra and removes the prostate with the internal sphincter muscle at the base of the bladder and the seminal vesicles, do we credit the surgeon who went ahead? To me these are the most startling physiological recoveries that I have ever seen in surgery. These men do get well. They get physiologically well, they have bladder control."

In 1942 Lloyd Lewis wrote: "When patients are properly selected the mortality rate should be almost as low as with benign operation. And most of these patients are advanced in years, infirm, many with severe cardiac disease."

A study of all cases of radical perineal prostatectomy at Johns Hopkins Hospital from 1904 to 1939 shows a hospital operative mortality of 5.8%. In Elmer Belt's series the operative mortality was 4%.

In 1935 Rolnick stated:

"Transurethral prostatic resection relieves the vesical neck obstruction but it also hastens the spread of the cancer and undoubtedly aggravates the other symptoms due to extension or metastasis. While resection establishes a groove, it hastens the spread of the growth by cutting through the lining mucous membrane of the urethra. Its value can be seriously questioned."

This opinion is shared by many leading urologists.

Dr. Reed M. Nesbit of the University of Michigan, one of the foremost advocates of transurethral prostatectomy on this continent stated in 1943:

"When the lesion is confined within the prostatic capsule, and does not show evidence of local or remote metastasis, perineal exposure of the prostate gland is clearly indicated. At the time of operation, material can be obtained for biopsy and frozen section analysis can immediately be made. If localized cancer is found, radical perineal prostatectomy should be performed."

ANDROGENS AND ŒSTROGENS

Approximately six years ago Kutscher, Wolbergs, Robinson, Gutman, Huggins and his coworkers described the results of their studies of the effects of the administration of androgens and œstrogens on the production of prostatic secretion in dogs. Androgens activate the prostatic epithelium with resultant increase in its production of prostatic fluid. Œstrogens were found to stop the production of prostatic fluid and also to cause a regression of the epithelial cells. As a result of these observations Huggins began to castrate men who had advanced carcinoma of the prostate and reported the almost miraculous clinical improvement that ensued. Not only did the primary cancer regress but the metastatic nodules melted away. It was not long before the literature was flooded with reports of treatment by orchiectomy or stilbœstrol or both combined. Unfortunately in many cases the immediate clinical improvement is only temporary, and in other cases so treated the clinical course was unaffected. Patients who run a long course before relapse have been termed "delayed failures". Sooner or later the disease will reactivate and claim its victim. No man has ever been cured by this treatment. Only adenocarcinoma of the prostate is improved by orchiectomy or œstrogens. Mixed and undifferentiated types respond less favourably or not at all.

In 1945 A. L. Parlow of the University of Rochester School of Medicine wrote that early cancer of the prostate should have the benefit of radical perineal prostatectomy. The case of the patient with advanced carcinoma of the prostate is a difficult problem. Metastases have occurred and the radical operation is considered as offering no permanent benefit. Bilateral orchiectomy, or the use of stilbœstrol, or their combined use with or without a per-urethral prostatectomy for obstruction of the vesical neck can be used. In 36 of 75 of his cases so treated by orchiectomy there was an apparent complete clinical disappearance of the cancer. It is in this group with remissions as a result of orchiectomy and œstrogen therapy that a radical perineal prostatectomy should be done. This opinion is shared by many eminent urologists.

The subject of perineal prostatic enucleation and of radical perineal prostatectomy has been and still is a controversial one. Dr. Hugh Young and the Young-trained urologists and their students favour it. Many prominent names have appeared among the opponents. This controversy has taken place in all the leading medical journals. As late as 1942 there was a query in the correspondence section of the *J. Am. M. Ass.*: "What is the surgical treatment of malignant neoplasm of the prostate?" the answer given was:

"It is the opinion among urologists that once the diagnosis of carcinoma of the prostate has been made it is technically impossible to do any sort of surgical procedure that will effect a cure. Thus when the diagnosis of cancer of the prostate has been definitely made the condition is no longer surgical."

This extraordinary statement brought forth replies from several urological surgeons of international repute, among them G. Gilbert Smith, Frank Hinman, G. Gordon Scannell, O. S. Lowsley and others. A statement by Young himself asserts: "a meticulous analysis indicates that more than 40% of patients followed for five years or longer after leaving hospital show no evidence of recurrence or of metastasis".

With the improvements in pre- and postoperative care, urinary antiseptics, and bowel preparation and sterilization that are available to us today I feel that any patient with carcinoma of the prostate suitable for radical re-

movable is being done a grave injustice to be deprived of his only chance of cure; 14% of all males past 44 years of age have cancer of the prostate according to Rich and Moore. Hinman states that 17 to 20% of males over 50 years have cancer of the prostate; 19% of untreated patients live 3 years, less than 4% are alive at the end of 4 years. Average duration of life is thus 22.7 months, although some patients do live 10 to 12 years. With metastasis present when first seen the life expectancy of an untreated case is 11.4 months. Most of these patients die from uræmia due to obstruction of the intramural portion of the ureters following invasion of the floor of the bladder by direct extension of the growth. Intestinal obstruction may also occur from spread of the cancer along the rectovesical layer of the pelvic fascia.

Young states that statistics show that carcinoma of the prostate is three times as common as cancer of any other internal organ in males. As the site of cancer in the male the prostate ranks 3 with the skin and the gastro-intestinal tract; 56% of cancer of the prostate can be diagnosed early by rectal examination; 75% start in the posterior lobes. Young states that carcinoma of the prostate is accompanied by benign hypertrophy of the lateral lobes in over 50% of cases and that the two lesions often grow side by side independently. Cancer can also develop in the posterior lobes after enucleation of an enlarged prostate or a transurethral prostatectomy which leave behind the capsule. Prostatotomy is a more correct term for these operations. The only prostatectomies performed are Young's radical perineal and the modified subtotal of Lowsley for benign prostatic hypertrophy, in which he leaves behind the seminal vesicles and ampullæ. Lowsley reports 9 cases of occurrence of carcinoma of the posterior lobes after the removal of the enlarged prostate but not the capsule.

To determine the cause of the incontinence of urine that some of his patients developed, Young undertook an intensive anatomical study. The external urethral sphincter was not injured at operation. This is the only sphincter left after suprapubic and transurethral prostatectomies and in most cases there is no incontinence. That it does occur after these operations we well know, even though the external sphincter muscle is not injured. Young's careful study of the anatomy showed that the anterior surface of the prostate was covered by a layer of fascia which separated it from the vessels and nerves of the space of Retzius. At operation he found that by blunt dissection this fascia could be separated from the anterior surface without difficulty and without opening into the prostate. There was also less hæmorrhage than with his original technique. The only other modification now adopted is the Vest suture method of anastomosis of the base of the bladder to the membranous urethra. Young stated in 1945 that since the adoption of these changes they have had no urinary incontinence in the last 7 years. The external sphincter is a voluntary muscle and a little effort in re-education on the part of the patient and the urologist is required as after any prostatic operation. At the meeting of the American Association of Genito-Urinary Surgeons in 1941 G. Gilbert Smith of Boston, Colston and Young of Baltimore, Deming of New Haven and Wear of Madison, among others, all favoured the radical perineal prostatectomy for carcinoma of the prostate, even if incontinence was to be expected in every case, with the necessity of wearing a penis clamp or urinal, the patient would be no worse off than if he had a colostomy!

Dr. Burnett Wright of the Vanderbilt University School of Medicine summarized the technical problem of prostatic surgery in 1941:

> "(1) There are indications for all the operations for relief of prostatic obstruction. These indications overlap it is true, but with more experience and closer study to determine the type and degree of obstruction preoperatively, the choice of operation can be made more definitely. (2) There is a very slight difference in the mortality rate in favour of the perineal operation over the suprapubic. In experienced hands transurethral prostatic resection is probably the safest of all, but has a high morbidity rate. (If a per-urethral or transurethral prostatectomy is done, I believe this latter factor can be avoided.) The postoperative functional results can be improved by choosing the operation best suited to the patient. (3) Every surgeon operating for prostatic obstruction should be qualified to recognize the various types producing prostatism and should equip himself to do all the operations with an equal degree of skill and safety to his patient and satisfaction to himself."

On the Urological Service at Shaughnessy Hospital we have performed 9 radical perineal prostatectomies for carcinoma of the prostate since January, 1946. The first two I did about one year ago. One of these patients we know has had no recurrence or metastasis. The other patient is due back for a recheck. We have had one operative death and another patient

has recently died of lymphosarcoma about 8 months after operation and no evidence of recurrence or metastasis of his prostatic carcinoma could be found at autopsy. Since October, 1946, four more radical perineals have been done. Our postoperative functional results have been good. These patients will have to be followed up. I am convinced that they have benefited from this surgery.

One of these patients I will now present as his case illustrates several points, one of which is the need for adequate and expert postoperative care and supervision.

Mr. W.A.T., aged 65 years. Admitted with surgical diagnosis of (1) hæmorrhoids, marked, bleeding, ulcerated and infected; (2) varicose veins, bilateral; (3) hernia, inguinal, right; (4) osteo-arthritis, chronic, back, shoulders and knees; (5) benign prostatic hypertrophy; (6) arteriosclerotic heart disease.

He was seen in consultation ten days after he had had a hæmorrhoidectomy done and was transferred to the urological service. He had had overflow incontinence for four days. An indwelling catheter was inserted for continuous drainage. His urological history dated back, five years. Frequency days 10 to 12, nights 2 to 4, with difficulty in starting his stream, poor force and dribbling. No change noted in his symptoms over the last five years until just prior to this hospital admission when he noted that they were all more marked. Rectal examination revealed a grade two plus glandular enlargement, smooth, not tender and not fixed. No evidence of malignancy.

The urine showed albumen two plus and white cells scattered to one plus and red cells one plus, culture showed diphtheroids and aerobacter aerogenes. Kidney function tests: 2 hour phenolsulphonphthalein test 25%; non-protein nitrogen 43 mgm. %; CO_2 87 vol. %. Red blood cells 4 million; white blood cells 20,000; Hb. 75%. Cystoscopy: (1) prostatism, marked, trilobed, large; (2) cystitis, marked, alkaline; (3) calculi, vesical; (4) calculi, prostatic; (5) review of I.V.P. showed hydronephrosis and hydroureter, bilateral, infected, with impaired kidney function.

A suprapubic prostatectomy was done in one operation. The patient made a good recovery and had a good functional result. The pathological report was: benign prostatic hypertrophy with a nodule of adenocarcinoma in the hypertrophied prostatic tissue.

The cancer was not in the posterior lobe and was not felt on the clinical examination. Acid phosphatase, 1.88 King-Armstrong units (0-3) alkaline phosphatase, 4.93 King-Armstrong units (5-10). Sedimentation rate 35 mm. per one hour (Westergren). K.U.B. films—no evidence of bony metastasis.

It was felt that this patient should have the benefit of a radical perineal prostatectomy and on November 25, this was done. This patient's perineum was very narrow and made the operation more difficult technically. Pathological examination of the prostate, vasa, and the seminal vesicles showed no evidence of malignancy. The night of the operation was uneventful but on the first day postoperatively the nurses' notes recorded at 10 a.m. "considerable pain and discomfort in operative region and over lower abdomen. Irrigation is satisfactory." When I first saw him he was pale and clammy, his abdomen somewhat distended and rigid and extremely tender over the lower portion. He had an intravenous running. His catheter irrigation was clear and appeared to be running satisfactorily except that it had backed up into the dripper of the irrigation setup. My diagnosis was extraperitoneal extravasation of urine and water accompanied by paralytic ileus due to peritoneal irritation. A Miller-Abbott tube was inserted, Wangensteen suction started, blood transfusion given, and the perineal wound opened widely for drainage. Only a slow drip was used through the urethral catheter. His intake and output, temperature, pulse and respirations, blood pressure, blood chlorides and non-protein nitrogen were closely watched.

The patient had several stormy days culminating on November 30 when there was great consternation on the ward as he complained of severe abdominal pain. Examination showed a normal blood pressure, a distended abdomen and in the Wangensteen suction drainage there was 20 oz. of dark brownish material. A hypo relieved the pain and one hour later, at 6.45 a.m., the patient expelled a large amount of gas and dark brown liquid feces with great relief. He made rapid progress after this evacuation. His perineum, where it had been reopened for drainage, broke down completely due to fecal contamination and it was necessary to do a secondary anastomosis of the bladder neck to the membranous urethra on December 9. His progress this time was uneventful.

He has a well healed perineum and good sphincteric control, his non-protein nitrogen is 31 mgm. %, Hb. is 90%, sedimentation rate 35 mm. Urinalysis of January 8, 1947, showed many pus cells and Gram-negative bacilli and Gram-positive cocci. Urine culture—heavy growth of *Aerobacter aerogenes*, a few *B. coli*, and moderate growth of *Strep. fæcalis*. We still have to eradicate this urinary infection and he will probably require a course of streptomycin later on. At the time of his discharge from hospital there was no evidence of recurrence or of metastasis.

SUMMARY

1. A brief review of the history of and clinical indications for radical perineal prostatectomy has been presented.

2. The prostate, as a site of cancer, ranks third after the skin and gastro-intestinal tract.

3. The necessity for routine rectal examination of all male patients for early diagnosis of carcinoma of the prostate is fundamental. There are no symptoms of early cancer of the prostate. It is the late effects, the complications of cancer of the prostate, narrowing of the urethra with slowing of the stream, congestion or ulceration of the mucosa with hæmorrhage, distant metastasis with physical depletion which at present far too often compel a rectal examination. Any patient of early middle age or later complaining of rheumatism or sciatica, unilateral or bilateral, should be suspected of having cancer of the prostate until ruled out by examination.

4. A case has been presented which illustrates (1) the necessity for careful gross and microscopic examination of prostatic tissue removed at operation. (2) The need for skilled male attendants as well as urological nurses.

BIBLIOGRAPHY

1. BELT, E., EBERT, C. E. AND SURBER, A. C. JR.: *J. Urol.*, 41: 1, 1939.
2. BELT, E.: *J. Urol.*, 48: 287, 1942.
3. BOYD, W.: Surgical Pathology, W. B. Saunders, 1944.
4. CALLENDER, C. L.: Surgical Anatomy, W. B. Saunders, 1939.

5. COLSTON, J. A. C.: *J. Am. M. Ass.*, **122**: 781, 1943.
6. DODSON, A. I.: Urological Surgery, C. V. Mosby, 1944.
7. GIBSON, T. E.: *Surg., Gyn. & Obst.*, **47**: 531, 1928.
8. HINMAN, F.: Principles and Practice of Urology, W. B. Saunders, 1935.
9. *J. Am. M. Ass.*, **118**: 855, 1942.
10. KEYES, E. L. AND FERGUSON, R. S.: Urology, 6th ed., D. Appleton-Century, Incorporated.
11. NESBIT, R. M.: Transurethral Prostatectomy, Chas. C. Thomas, 1943.
12. PEARSE, R. AND MEYER, E. G.: *Canad. M. A. J.*, **55**: 441, 1946.
13. Transactions of American Association of Genito-Urinary Surgeons, 1941.
14. WRIGHT, B. W.: *South. M. J.*, **34**: 751, 1941.
15. Year Books of Urology, Year Book Publishers, 1943 to 1945.
16. YOUNG, H. H.: Practice of Urology, W. B. Saunders.
17. *Idem*: *J. Urol.*, **53**: 183, 1945.
18. LOWSLEY, O. S. AND KIRWIN, T. J.: Urology, Williams and Wilkins, 1945.

925 W. Georgia, Vancouver, B.C.

EMOTIONS AND HUMAN RELATIONS*

H. O. Foucar, B.A., M.D., F.I.C.S.

London, Ont.

MAN is a machine, a most complicated machine; he is self-perpetuating and grows from a small beginning into a most complex form with many organs and many functions. He develops from a phase of absolute dependence on others to a stage of independence within an organized society, the complexity of which also varies greatly.

This necessitates many mental adjustments and results in many conflicts within the individual before he is able to take his proper place among his fellows. On his ability to adjust will depend in large measure his usefulness in the community. Those responsible for aiding in these changes are chiefly the parents, the teachers and finally the people in general with whom the individual is thrown in contact.

In the final analysis, man is judged by his actions, which represent the end product of this great machine. This is so important that it has been made the chief study of one school of psychology — the mechanistic or behaviourist school. These psychologists became tired of the introspective study of the processes of the mind, so they started with the end product and worked backwards. They studied the simple and more complicated reflexes and also the conditioned reflexes until, for many of them, an individual is a glorified robot. Given a certain stimulus there will be a certain response. For them, mind or even consciousness is non-existent.

It was recognized that pure sensori-motor reflexes are not sufficient in themselves to explain behaviour patterns, because the direct motor responses to the stimuli would be distinctly limited in scope. An intermediate reaction is necessary which accentuates the end reaction. Stimuli reach substations in the brain, known as the thalamus and hypothalamus, resulting in an emotion. This emotion in turn sets free energy which results in a more intense and prolonged response. Emotion has been called the motivator or driving force of behaviour. It may be likened to the detonator in an explosive charge. The explosive charge has great potentialities which lie dormant until activated by the detonator. The detonator, on the other hand, is most active and responds to simple contact.

From the thalamus, the centre of emotion, nerve fibres pass to the hypothalamus and thence to the sympathetic nervous system and to certain ductless glands, such as the adrenal. These in turn affect the muscles of the heart, blood vessels, stomach and intestines, skin and hair. This subject has been studied extensively by psychologists, especially by Cannon. He believes that emotional or affective reactions, such as fear, sorrow, joy and rage are mediated in the adjacent thalamic centres and that the process extends also to the hypothalamus, which through connections with the sympathetic nervous system, produces visceral changes. Indeed, the latter reactions are so definite that emotions can be defined psychologically in terms of reaction patterns, some of which are somatic (*i.e.*, pertaining to the framework of the body) and others visceral (*i.e.*, pertaining to the organs). Thus, the external signs of rage include "the crouching body, the moist or frowning brow, firm lips, clenched or grinding teeth, the growled threats or imprecations and the tightened fist, or the seized weapon ready for attack" (Cannon). The visceral reactions include cardiac acceleration, redistribution of blood, polycythæmia, contraction of the spleen, increased respiration, dilatation of the bronchioles, increased blood sugar, reduction in the blood coagulation time, dilatation of the pupils, etc. These reactions on the sympatho-adrenal system are important in fitting an animal for defence or flight, for attack or pursuit. These reactions are inborn; they do not need to be acquired. They have all the characteristics of unconditioned reflexes and differ from simpler ones only

* Read before the Current Topic Club, London, Ontario, January 25, 1947.

in their greater complexity (Wiggers). It has been suggested that certain conditions in man, *e.g.*, the manifestation of fear in shell-shock, the unreasoning rage of drunkenness and the emotional instability of certain mental derangements, associated with degenerative changes in the cortex may be due to release of the hypothalamus from the cortical control (Best and Taylor).

There are also connections between the thalamus and the frontal lobe of the brain which are important in the affective tone of the higher intellectual processes. These are the nerve fibres which are cut in the operation of the prefrontal lobotomy in certain mental diseases (Freeman and Watts).

Emotions are natural and basically protective but may become destructive if the resultant behaviour is not properly directed and controlled. We cannot prevent emotions but we can learn to control our response to these emotions. Our reactions may be primitive or mature, depending on our training. Because of the important place of emotions as motivators of behaviour, we should stress the need for proper understanding and training.

How much emotion the fetus experiences while floating in the amniotic fluid and attached to the maternal uterus is difficult to say. At this stage the individual is as secure as he will ever be. He is fed and housed with no effort on his part, but he is absolutely dependent. At birth he is rudely pushed out into this world and life becomes a new and expanding experience culminating normally in autonomy. The pattern of life is laid down in these early years. Much, therefore, depends on the parents. The infant is born, cared for and then weaned. It is right that he should be helped, protected and given a sense of security, but he must also be given a sense of responsibility. The weaning process must continue until the child has matured and has learned to stand on his own two feet, to make his own decisions and finally to strike out for himself and live his own life independently. Many problems arise where parents are too possessive. Often, but not always, faulty emotional reactions in an individual can be traced directly to the parents and home surroundings.

The prime object of education is not merely the accumulation of a fund of information but how to live with other people and this involves essentially the control of emotions and of behaviour.

The science of psychology is relatively new. Until recently it was vague and not of much value, because the discussions were too abstract. Strides have been made and now we know better why we act like human beings and we have a powerful tool in solving many problems, thus helping individuals to live a more stable and fuller life. As individuals are helped, so the community ultimately benefits. Huge regions, however, still remain unexplored.

The name of Freud occupies an important place in psychology. In 1895 Breuer and he studied hysteria and they described Breuer's method of catharsis. In 1900 he wrote on dream interpretation. He introduced the term psycho-analysis and replaced hypnosis by a method of "free association". He stressed sex as the driving force and therefore the primitive emotion. That sex is important, no one can deny but to explain everything on that basis is no longer acceptable.

Some of the ancients linked sex with the concept of immortality and worshipped it as such. It is true that certain objects which mean little to us may have had their origin in phallic worship, *e.g.*, obelisks. The horse-shoe as a good luck charm is said to be derived from the external female genitalia. Some see even in stately cathedrals the expression of this same phallic worship. People enter the labia, pass into the vestibule, down the vagina to the cervix (altar), while on each side stretch the tubes and ovaries. Even the windows and spires are given special significance. To most of us this seems fantastic and unnecessary and the figment of a warped mind. What is easier than to explain the building on the basis of architectural necessity?

In the final analysis, anything which touches our security in any field stirs up emotions. Many reactions can be traced directly to economic and social insecurity and may not even remotely be linked with sex, never mind in how broad a sense we may use the term. In interpreting dreams, many of them appear to be linked very directly to events of the preceding day or to physical states at the time of sleep. To these psychologists must go credit, however, for focussing attention on emotions and mental conflicts as factors in behaviour—normal and abnormal—and also as the cause of certain physical complaints.

All the mental conflicts that beset human beings may be reduced to the elemental drives that arise from the respective claims of the three great complexes—ego, sex and herd. For the individual there are infinite variations (Strecker and Appel). It is easy to see how some of these urges may be diametrically opposed, as exemplified by the soldier at the front forced to choose between self-preservation and the preservation of the herd.

Throughout life there are many such conflicts which result in varying degrees of emotional stress. These conflicts may occur within the different planes of consciousness. It may be in the zone of full consciousness when the individual realizes the factors and wavers between them. If in the zone of subconsciousness, he may be only vaguely cognizant of the cause of tension. In the unconscious realm, the offending experience has been pushed deep down and it is only with difficulty that it can be linked with the particular behaviour pattern.

As long as we live there will be mental conflicts. We cannot escape this. Our behaviour will depend on our method of adjustment. Early in life a child should be taught to face facts and to make choices and, having made these choices, to be content. Rarely is it possible to have everything. It is usually a matter of either . . . or. It is important that all should develop a balanced healthy philosophy, as Cabot suggests, of work, play, love and worship.

Love is one of the great emotions and, within bounds, it is constructive. It may vary in degree and may appear in many forms. An individual likes himself and is careful for his well-being. He loves his family and is loyal to his friends and community. He may show great patriotism for his country or he may adopt a good cause and devote his energies to it. It is no exaggeration to state that most of what is good in this world stems from this emotion.

Fear is protective. It results from whatever interferes with or even threatens our sense of security whether in the field of ego, sex or the herd. The race would soon disappear if individuals had no fear. It has been said that the two primary fears are those of falling and of sudden noise and that all other fears are acquired. Children learn early from others or from their own experience. They are afraid of dogs because the mother is, or because they have been bitten. The natural response to fear is flight. In flight the emotions are discharged, the tension lessened and the situation may be saved. In human existence, flight is not always possible and tensions occur which may have strange and far-reaching effects.

There are times when fear for one's personal well-being must be submerged and aggressive action must be taken for one's own good or the good of others. Herein lies the difference between bravery and cowardice. Fear is a natural emotion which cannot be prevented. The action taken, however, will depend on training and discipline.

Many fears are due to ignorance. The prevention of fear then is knowledge. When we are familiar with a phenomenon, we often lose fear because we have learned how to cope with the situation. Where we have no personal knowledge, we may have faith—faith in our parents, our leaders and finally in a deity. We may not know the answer, but we are content to throw the burden of responsibility on someone else. Unhappy indeed is the person who lives perpetually in a world of phobias. We fear or are suspicious of other countries partly because we do not know the language or the conditions. If there were a universal language much international unrest would disappear.

Anxiety is only fear in another form. For mental health, some form of confessional or mental catharsis seems necessary. The devout pour a recitation of their sins and worries into the ear of a priest in confidence. They receive advice, do penance and feel relief from what would otherwise oppress them. The Oxford Group have a similar mechanism which they call sharing. Ministers, doctors and teachers at large often perform this same function.

Doctors frequently are called on actively to probe the minds of patients in search of the solution to certain physical problems. This is being realized more and more and now we recognize a new subdivision of medicine—psychosomatic medicine. We now know that many physical symptoms have their origin in emotional disturbances. These patients do not require medicines or operations, but will be relieved when the underlying emotional tension has been eased.

The solution in many cases is difficult and time-consuming. During the depression and then during the war, I developed the habit of asking my patients whether anything was

worrying them. It was surprising how often anxiety in some form or other was present, fear of disease, whether of cancer, tuberculosis or heart trouble, financial worries, anxieties in connection with their job, concern for relatives overseas or for troubles within the family. This emotional tension was often directly responsible for the symptoms present. The more difficult cases will require special investigation by experts by means of psycho-analysis, narco-analysis and free association of words.

At this point, it might be well to say there is a limit to any man's power of endurance. Hunger, cold and fatigue may all accentuate fear reactions. This was seen overseas in so-called battle fatigue. Here it was found that prompt recoveries were often made without removing the man from the sound of battle by using heavy sedation, inducing sleep. During this drowsy state the man was encouraged to discuss his experiences, instead of pushing them into his subconscious mind.

Recently a man presented himself at my office with symptoms suggestive of an early ulcer of the stomach. X-ray examination, however, was negative. What was the cause of his trouble? A little questioning unearthed the eternal triangle. He had been going with a girl for some time. She broke it off. He married someone else and then went overseas. On his return he found that both he and his wife had changed. He suddenly met another girl. It was for both of them love at first sight. What can he do about the situation? His stomach will stay churned up until he works out his solution. Medicine will be of little value.

Twenty years ago a patient came because a high-ranking internist had said that she needed her ovaries removed. Why, it is hard to say in view of her history. She had periodic attacks of headache and vomiting and she was losing weight. More recently she complained of abdominal pain suggestive of kidney colic. She admitted that she was worse when she worried. What was her story? She was a music teacher who could not find pupils. To eke out an existence she had to keep a boarding house, something she did not like. Recently she told me that she had never known what it was to be able to pay an account when it was due. Her physical symptoms always occurred when she had financial obligations to meet. An operation would only have made her worse because it would have added to her load. She has improved because she understands her problem.

A girl was told that she had a toxic goitre and needed her thyroid removed at once or she would die. She was alarmed by this as were her parents. She was thin and nervous and had a rapid pulse but other important features of thyroid disease were absent. In questioning her I found that she was engaged and that her boy friend was drinking rather heavily and this worried her tremendously. She was given a mild sedative and told to talk things over with her friend. They evidently worked out a solution for they are now married and she is happy, gaining weight and her pulse is normal.

Many cases of migraine, insomnia and nervous exhaustion are emotional in origin. It is of no use to say that there is nothing wrong or that it is all due to imagination. If these cases are to be really benefited they require emotional readjustment.

Anger inherently is the impulse to kill or destroy. The preservation of an animal depends on its ability to kill or its ability to run and hide. Both are necessary and protective. The emotion is aroused reflexly and as such cannot be stopped. The behaviour pattern, however, can be controlled. There are many reactions to anger. Some people explode with each stimulus. This may be a little hard on others but it relieves personal tension, except in so far as remorse or regrets may be built up on account of unwise behaviour. Others may ignore or suppress many stimuli and then suddenly explode over some trivial incident and some relatively innocent party. Psychologists say that we should face facts and then do something about it instead of repressing the experience only to have it reappear in a different form later. Hyde Park Corner in London is a unique institution. Here an opportunity is given people to blow off steam. It is a national safety valve which prevents serious explosions.

We have already stressed that there will always be mental conflicts. Strecker and Appel enumerate a number of typical ways of meeting these conflicts, some sensible and some the reverse.

1. Regression.—This is a primitive childish type of reaction. A man bumps into a wall in the dark. He kicks and swears violently. The behaviour is not rational. It is surcharged with emotion. The unchanged problem still confronts him. The regressive action is ineffective and procrastinating, often it is humiliating. The emotional outburst is a relief but it accomplishes nothing constructive.

2. Extroversion.—The mind tries to distract itself by the assumption of feverish activity, pacing up and down, talking beyond the point, passing from one activity to another. It may be a useful method of meeting mental dissatisfaction and complexes. Sometimes extroverted activity is purposeful, useful and constructive, and sometimes it is the reverse. The man has run away and has attempted to cover his flight from himself and others by a tremendous burst of activity.

3. Introversion.—Thought de-energizes situations and conflicts. A tense situation can often be rendered more or less harmless by thinking about it. Thinking employed to check spontaneous and hasty action and to clarify issues is fulfilling its proper function. When, however, it is used to dodge issues and avoid making decisions that should be made it is not only not performing its proper service, but it is also untrue to its own *raison d'être*. If carried too far nothing is ever done, for it is much easier to imagine things are so than to make them so.

4. Rationalization.—This is mental camouflage. It is the habit of thinking which gives plausible reasons rather than actual ones for our thoughts and behaviour. When true motives are not recognized we are likely to have rationalization. It is a form of self-deception. It is not a satisfactory method of handling conflicts. It is better to recognize the difficulties and plan our actions clearly and effectively. The first problem is to get people to face the facts squarely.

5. Segregation or the development of logic-tight compartments.—Barriers may prevent one side of the personality from observing what the other side is doing. An example is found in the case of "Dr. Jekyll and Mr. Hyde". It is also seen in the split personality of schizophrenia.

6. Repression.—We all like to forget the unpleasant and painful experiences in life. There are two ways of forgetting, passive and active. The things that are forgotten in the second method are matters to which a strong and often disturbing feeling is attached. The tendency that is submerged is said to be repressed. Segregation is dissociation at one level of the mind. Repression is dissociation at different levels.

7. Dissociation.—Whenever an emotional disturbance follows some trifling or insignificant incident, we may be sure that some complex is aroused. The trifle is the spark to the fuse.

8. Conversion of mental conflicts into physical symptoms, anxiety, neurasthenia and hysteria. This has already been touched on.

9. Mental use of substitutes.—Transference of emotions and the importance of symbolism.

10. Projection or fault finding and shifting the blame. —We may avoid recognizing our deficiencies and faults by attributing them to others or to the nature of things. In this way we may deny our weakness or responsibility.

11. Identification.—We identify ourselves as closely as possible with people and institutions that represent for us ideal qualities. Both projection and identification constitute psychological magic employed by the mind to bring peace, harmony and happiness into life. Identification possesses more potentialities for good than projection and carries with it fewer dangers. Its chief dangers are in the direction of excess.

12. Inferiority complex and compensation.—This is a common reaction. Disappointment, failure, defeat and infirmity are the common seeds of the inferiority complex.

13. Sublimation.—What has been described so far are methods utilized to escape the frank facing of the conflicts or mental hazards which result from warring of our complexes. They are all crutches which enable us to walk mentally. There is one way of walking mentally upright without crutches and it is called sublimation. It consists in facing facts squarely, and if we are prevented from doing one thing, then diverting that energy to some other socially useful purpose.

It has seemed to me that the whole answer to human relations is human behaviour and this is based ultimately on the behaviour of the individual. The emotions which affect the unit also influence the whole. Mentally healthy leaders advance civilization, while warped individuals given power, may jeopardize the future of the world.

In closing I can do no better than to cite Osler's remarks at a farewell dinner when he was leaving Johns Hopkins for Oxford in 1905. He is an excellent example of a man who was emotionally stable.

"I have had three personal ideals. One, to do the day's work well and not to bother about tomorrow. To it, more than to anything else I owe whatever success I have had—to this power of settling down to a day's work and trying to do it well to the best of one's ability and letting the future take care of itself.

"The second ideal has been to act the Golden Rule as far as in me lay, towards my professional brethren and towards the patients committed to my care.

"And the third has been to cultivate such a measure of equanimity as would enable me to bear success with humility, the affection of my friends without pride and to be ready when the day of sorrow and grief came to meet it with the courage befitting a man.

"What the future has in store for me, I cannot tell—you cannot tell. Nor do I care much, so long as I carry with me as I shall, the memory of the past you have given me. Nothing can take that away.

"I have made mistakes but they have been mistakes of the head, not of the heart. I can truly say, and I take upon myself to witness, that in my sojourn among you:—

> "I have loved no darkness,
> Sophisticated no truth,
> Nursed no delusion,
> Allowed no fear."

BIBLIOGRAPHY

1. BEST, C. H. AND TAYLOR, N. B.: Physiological Basis of Medical Practice, Williams & Wilkins, Baltimore, p. 1491, 1943.
2. CABOT, R. C.: What Men Live By: Work, Play, Love, Worship, Houghton Mifflin Co., Boston, 1914.
3. CANNON, W. B.: Bodily Changes in Pain, Hunger, Fear and Rage, D. Appleton & Co., N.Y., 1934.
4. *Idem*: *New England J. Med.*, **198**: 877, 1928.
5. FREEMAN, W. AND WATTS, J. W.: Psychosurgery, Intelligence, Emotion and Social Behaviour Following Prefrontal Lobotomy for Mental Disorders, C. C. Thomas, Springfield, Ill., 1942.
6. FREUD, S.: Introduction to Psychoanalysis, Boni & Liveright, New York, 1920.
7. JUNG, C. G.: Contribution to Analytical Psychology, translated by H. G. and C. F. Baynes, Harcourt, Brace & Co., 1928.
8. OSLER, SIR W.: Æquanimitas, Blakiston Co., Philadelphia, Pa., p. 450, 1943.
9. STRECKER, E. A. AND APPEL, K. E.: Discovering Ourselves, Macmillan Co., New York, 1931.
10. TRUDEAU, E. L.: An Autobiography, Lea & Febiger, Philadelphia, Pa., 1916.

La pipe donne l'air bonhomme; le cigare, l'air important; la cigarette, l'air gamin: tout cela ne présente que variétés de sucs.—*L'Action Médicale.*

CASE REPORTS

EOSINOPHILIA WITH TRANSIENT LUNG INFILTRATION (Löffler's Syndrome)*

D. A. Rice, M.D. and J. W. Scott, M.D.

Edmonton, Alta.

The association of transient infiltrations of the lungs and eosinophilia was first noted by Löffler[1] at Zurich in 1932. Since that time a number of cases of this syndrome have been described, most of them in the European literature. Löffler's syndrome is characterized by symptoms of pulmonary disease with clinical and radiological signs of lung infiltration. The most striking part of the picture however is the rise of eosinophilic polymorphonuclear cells in the peripheral blood.

The patient showing the condition is not acutely ill as a rule and the illness runs a benign course of from two or three weeks to as many months.

The following case history describes, we believe, a typical example of this interesting disease complex.

A 40 year old white woman was admitted to the University of Alberta Hospital on April 28, 1945. She complained of loss of energy for three weeks, a non-productive cough for three days, with profuse night sweats.

The past history revealed no evidence of previous illness. She had been free from respiratory and allergic disease. The patient had not lived outside Canada. Examination showed a normal temperature throughout her two weeks' stay in hospital. Physical examination of the chest on admission showed crepitations scattered throughout the bases of both lungs. An x-ray examination of the chest on admission showed infiltration at both lung roots, radiating out to the periphery on the right side (Fig. 1).

The blood count on admission showed red blood cells 3,600,000, hæmoglobin 11.3 gm., white blood cells 8,850, neutrophils 23%, eosinophils 51%, lymphocytes 20%, monocytes 6%. The urinalysis gave normal findings. The sedimentation rate was 17 mm. in one hour (Cutler). Repeated examination of the stools showed no ova or parasites. The skin tests were positive for tuberculosis and negative for brucellosis. No sputum could be obtained for examination.

Skin tests were carried out for a number of seasonal pollens and common foods with negative results. The basal metabolic rate was –15%. The blood Wassermann was negative. There were no symptoms or signs suggesting trichinosis.

The patient improved subjectively and was discharged from hospital two weeks after admission. The physical signs in the chest had disappeared and x-ray examinations of the chest showed progressive lessening of the hilar infiltration (Fig. 2).

Table I indicates the hæmatological findings over a period of five weeks. Blood examinations carried out on the mother and sister of the patient showed no evidence of a familial eosinophilia.

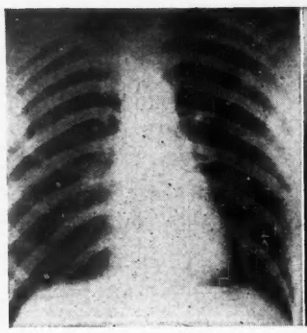


Fig. 1

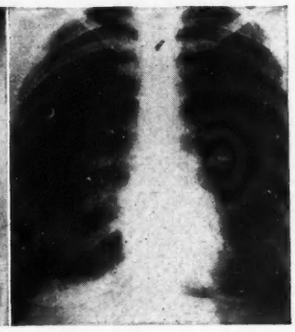


Fig. 2

TABLE I.

Date	*W.B.C.*	*Eosinophils %*	*Neutrophils %*	*Basophils %*	*Lymphocytes %*	*Monocytes %*	*Sedimentation rate mm./hr.*
May 14, 1945.....	8,850	51	23	0	20	6	17
May 19, 1945.....	8,900	37	37	0	24	2	..
May 22, 1945.....	11,150	35	37	0	22	5	..
May 24, 1945.....	10,000	34	36	0	24	6	..
May 26, 1945.....	10,000	30	30	0	32	8	..
June 2, 1945.....	8,000	18	47	0	30	5	..
June 6, 1945.....	6,800	24	35	0	38	3	8
June 9, 1945.....	6,000	20	36	0	40	4	..
June 13, 1945.....	6,300	19	32	0	46	3	..
June 18, 1945.....	13,050	16	69	1	11	3	10
June 20, 1945.....	10,000	20	45	1	31	3	..

DISCUSSION

It has been suggested that the lung infiltrations and eosinophilia of Löffler's syndrome indicate an allergic manifestation. In our patient as in many of the other cases reported no allergen could be demonstrated as a causative factor.

Various allergenic agents have been described in the reported cases of Löffler's syndrome, including the larvæ of *Ascaris lumbricoides*, the tubercle bacillus, brucella organisms, *Endamœba histolytica*, *Ancylostoma braziliense* and a variety of pollens. As the disease runs a benign

* From the Department of Medicine, University of Alberta, University Hospital, Edmonton, Alta.

course, with recovery in most instances, there have been few opportunities to study the lung lesions at autopsy. Two such examinations have been reported.[2, 3] In both instances the lung lesions indicated a lobular pneumonia with an alveolar exudate rich in eosinophils. Giant cells were present.

The eosinophilic blood level in the reported cases has ranged from 10 to 60% and it is of interest that the degree of eosinophilia does not parallel the degree of lung infiltration. Further, the highest levels of eosinophils in the blood may occur when the lung shadows are disappearing radiologically.

Löffler's syndrome may be confused with pulmonary tuberculosis and atypical pneumonia. However, the prompt roentgenological improvement and the striking eosinophilia help to exclude the latter conditions.

SUMMARY

A case history is presented in which eosinophilia and transient lung infiltrations were presenting features.

The clinical, radiological and hæmatological characteristics of Löffler's syndrome, of which we believe this is an example, are discussed.

REFERENCES

1. LÖFFLER, W.: *Beitr. z. Klin. d. Tuberk.*, **79**: 368, 1932.
2. VON MEYENBURG, H.: *Schweiz. med. Wchnschr.*, **72**: 809, 1942.
3. BAGGENSTOSS *et al.*: *Proc. Staff Meet. Mayo Clinic*, 457, 1946.

MITRAL STENOSIS AT THE AGE OF 81

John M. Tainsh, L.M.C.C., M.B., M.R.C.P.(Lond.), F.R.C.S.(Eng.)*

Cochrane, Ont.

The patient, Mrs. M.W., was admitted to King George Hospital on April 22, 1946. Her complaint was of severe abdominal colic and vomiting which had commenced 24 hours previously. She had been confined to bed for the last four months suffering from congestive heart failure from which she had almost recovered. Past history was rather vague as she was simple-minded and relatives were unable to give much information. Her age of 81 was officially established when her old age pension was first granted. She was a widow and had 6 children. Her health had been good, she suffered from rheumatic fever in the early 1900's and was treated in the London Hospital. She had one other illness of an uncertain nature for which she was treated in the North Middlesex County Hospital in 1939. No history of heart failure was obtained previous to 1946.

On examination she was a frail elderly woman with mild pitting œdema of her ankles. She had moderate abdominal distension with visible peristalsis secondary to a strangulated right femoral hernia.

The cardio-vascular system.—Her pulse was irregular, the rate varying between 130 and 140, her blood pressure was 180/100 (as near as could be estimated in the presence of fibrillation) and she had marked venous pulsation of the neck. The apex beat was diffuse and displaced markedly to the left. Auscultation revealed a rough systolic murmur heard all over the precordium and a very typical triple rhythm due to a mid-diastolic murmur. There were no other abnormal physical findings.

In view of the severity of the abdominal symptoms I operated at once, doing the routine herniotomy using local infiltration anæsthesia with novocaine. Fortunately, the strangulated loop of ileum was viable and the operation was completed without difficulty. No ascitic fluid was seen when the sac was opened. At the termination of the operation she was given 0.5 mgm. digoxin orally every six hours until the 4th day when nausea occurred. The digoxin was then stopped and on the next day gr. 1 of digitalis folia was commenced and given daily. The pulse remained between 70 and 80.

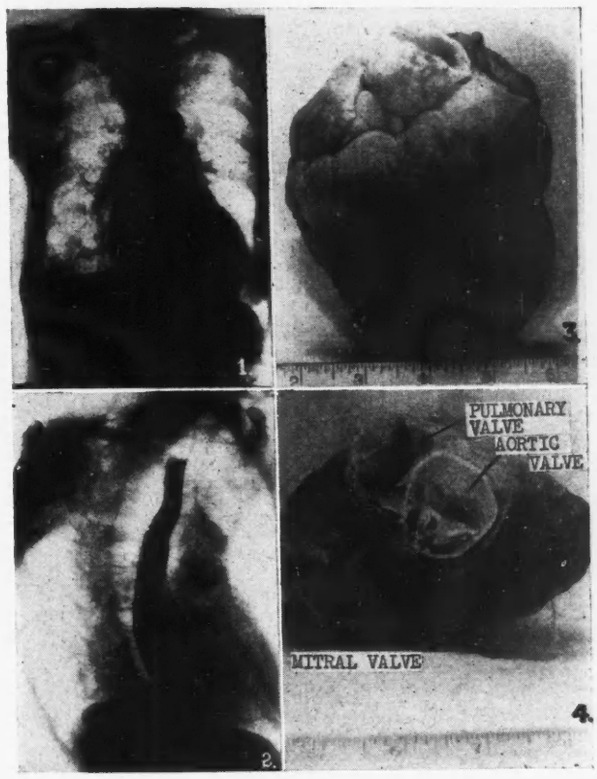


Fig. 1.—P.A. view of heart. **Fig. 2.**—R.O. view of heart with barium swallow. **Fig. 3.**—General view of heart. **Fig. 4.**—View of heart to show deformed valves.

She was fit for screening on the 13th day after operation. The findings were as follows:

P.A. view.—Enlargement of the left ventricle: enlargement of the pulmonary conus, and deflection of the barium swallow to the right (by the left auricle).

L.O. view.—Marked enlargement of the left ventricle.

R.O. view.—Prominence of the pulmonary conus. Enlargement of the left auricle, well demonstrated by the backward deflection of the barium swallow.

The electrocardiogram showed left axis deviation with depression of the ST segment due to digitalis effect.

On clinical and x-ray evidence a diagnosis of mitral stenosis complicated by benign hypertension was made. The patient was discharged in good condition on May 6.

* Late Surgical Registrar, King George Hospital, London, England.

A later report from Dr. J. A. Keeling states:

"Mrs. W. was re-admitted on August 9 and died on the 12. On admission the cardio-vascular clinical signs were unchanged from those of her previous admission except that she had gross œdema of her limbs and back, with evidence of a bilateral hydrothorax with pulmonary œdema, blood pressure 140/80, slow fibrillation, apical thrill, long low rumbling murmur replacing the 1st sound and a triple rhythm. No aortic murmur was detected.

"The condition of the heart at autopsy is shown by the accompanying photographs: left ventricular hypertrophy, button-hole mitral valve stenosed and incompetent, marked aortic stenosis with fixed calcified cusps. The tricuspid and pulmonary valves were normal. The coronary arteries show moderate sclerosis. Bilateral hydrothorax was present with a small left basal pulmonary infarction. Findings of chronic venous congestion in all other organs. This old lady's survival to the age of 81 years with such a degree of structural damage must certainly be most remarkable."

I have thought this case worth publishing, firstly because of the extreme rarity of mitral stenosis at this age, and secondly because it shows that heart disease in the elderly is no bar to necessary surgical procedures.

I wish to thank Mr. Neil Sinclair, F.R.C.S. (Senior Surgeon of King George Hospital) for permission to publish this case and also Dr. J. A. Keeling for permission to quote from his letter and to use his photographs of the heart.

EARLY TUBAL PREGNANCY

Robert Kerr Dewar, B.Sc.(Edin.), M.D.(Man.), L.M.C.C.

Fort William, Ont.

As Hamilton Bailey remarks in his *Emergency Surgery,* most tubal pregnancies seem to be diagnosed after complete rupture, and some of these could certainly be prevented. I think, indeed, that one of the difficulties encountered in our weighing the diagnosis in the present case was caused just by the very off-hand skepticism of colleagues who, though most helpful in every way, were inclined nevertheless to doubt that a tubal pregnancy such as this could be diagnosed at such an early stage.

Mrs. A.S., about 35 years of age, was seized with very severe stabbing pains in the right lower abdomen. She was two weeks overdue with her periods, though previously always very regular. The history was so typical that even over the telephone I suggested the probability of tubal pregnancy, and so diagnosed it tentatively. Consultation at six o'clock that evening in Port Arthur General Hospital, showed patient crying with pain, writhing in distress, but with no appreciable mass on pelvic examination. Pulse was strong, 60 per minute, and temperature subnormal. Consultant advised watchful but careful waiting, and further examination. Urinalysis, plain x-ray of abdomen, and routine tests were negative, and during the next 4 days patient developed occasional severe stabbing pains low on the right side, below the usual area associated with appendicitis, and whereas on occasion the abdomen would become quite tense, at other times it would be normal. Once it was the left side which became rigid, the right subsiding. This gave rise to the speculation of ordinary salpingitis, but penicillin in 100,000 units daily, rising to 150,000, tended to rule this out: also the normal temperature. Finally, on the fourth day, patient developed an exacerbation of the severe right-sided pain which promptly subsided, but the white cell count was 24,700, and it was this which convinced us that there must be free blood in the peritoneal cavity. AZ test was considered, but not done in time.

On the morning of the fifth day, with general anæsthesia commencing with pentothal sodium intravenously, and maintained by open drop ether and chloroform, and then cyclopropane anæsthesia, the abdomen was opened by right paramedian incision, which had to be of fair length due to unusual stoutness of patient. For the same reason, it was found impossible to visualize the pelvis, but a hand introduced into the right side of pelvis showed dark red thick blood on withdrawal. Diagnosis of right tubal pregnancy leaking slightly was thereupon confirmed. As concomitant left tubal pregnancy is not infrequent, the left tube was palpated, but seemed normal. The right tube was located by touch alongside a normal ovary as having a slightly-bulbous end, and was drawn up into the wound, where a typical early tubal pregnancy was found, not much larger in size than a normal appendix, but with free blood slowly oozing from the ostium, and with the whole red-blue and intensely congested in colour, with swelling over the position of fetus. The terminal end of the tube was removed after interlocking sutures on pedicle, and after dusting in sulfathiazole powder, the abdomen was closed without drainage. Recovery was uneventful.

Now comes the thought which is based on 24 years of experience as family doctor, namely, that most of these cases just do not need to happen in the first place if precautions are taken at the very outset to eliminate chronic infection in the uterus and tubes which is, in my opinion, the cause of the great majority of tubal pregnancies. Now, I am quite aware that there is an infinite variety of recommended treatments, but I want to suggest a treatment which has been developed by myself, and which has stood the test of time and over fifty thousand individual treatments over a period of the past quarter of a century of private practice. In some ways it bears resemblance to what used to be done by such men as the late Dr. Franklin Martin of Chicago. Suffice it to say that as a result of this treatment I have never encountered any severe reactions or untoward results, and if ordinary care is taken to exclude pregnancy, and to use gentleness, especially at first until familiarity with the method is attained, there is no appreciable discomfort to the patient.

I use either short-wave diathermy or long-wave to the cervix which can be administered by a vaginal stem electrode of metal, insulated on the shaft by a shield of vulcanite or rubber, with an outside neutral electrode of sheet lead on the abdomen in long-wave; a strap rubber electrode—both of these laid on skin above pubis—in short-wave diathermy. I use long

and short-wave alternately, though long-wave at present requires radio-proofing of the room by metal shielding under Federal law. Generalized ultra-violet irradiation of the whole skin is most important over weeks and months to build up body resistance to the infection. I treat with diathermy anywhere from an hour to a day all the way from once a week to daily, depending on severity. In endometritis I put a thin curved metal probe into the uterus, cotton-wound, and very thin; cotton tight on it; bathed in one-third strength tincture of iodine, excess taken off.

SUMMARY

A case of tubal pregnancy is outlined. Tubal pregnancy is discussed as a sequel to chronic infection of tubes and uterus, and a method is outlined for treating the uterus with medication and electric current.

MILIARY TUBERCULOSIS TREATED WITH STREPTOMYCIN

R. H. Craig, M.D.

Essex County Sanatorium, Windsor, Ont.

Thus far, few reports dealing with the effect of streptomycin on miliary tuberculosis have appeared in the literature. In July, 1946, Bornstein, writing in the *Sea View Hospital Bulletin* described the effect of streptomycin on a four year old child with miliary tuberculosis and tuberculous meningitis. Its beneficial action was shown by the regression of meningeal symptoms and marked clearing of the lung fields. Unfortunately, about a month after withdrawal of the drug, the meningitis recurred and progressed despite further intensive streptomycin therapy to a fatal termination.

In view of this encouraging report it was decided to employ streptomycin in a rather early case of miliary tuberculosis which came to our notice five months ago.

The patient, a twenty-five year old white male, was discharged from the army in March, 1946, with an apparently negative chest x-ray. He returned to work and remained in good health until May 8, 1946, when he developed a pain in the left upper abdomen followed by malaise and fever. He was eventually admitted to Camp Borden Military Hospital with a diagnosis of left-sided pleurisy with effusion. A thoracentesis yielded 600 c.c. of fluid and he was later transferred to Christie Street Hospital where he continued to exhibit a low grade fever.

On July 3, 1946, he was admitted to Essex County Sanatorium. The patient was seen to be a well nourished, well developed adult male weighing 185 lb. Except for an occasional dry cough, he had no complaints. Physical examination except for the chest was not remarkable. Temperature was 99°; blood pressure 120/95.

Examination of the chest disclosed impairment of resonance over the basal half of the left chest decreasing toward the apex. Breath sounds were absent at the base. A pleural friction rub was audible anteriorly and posteriorly. The right side showed no abnormality.

X-ray on admission showed evidence of a left-sided pleural effusion with evidence of pleural thickening extending up the chest wall laterally to the cupola. There was no evidence of parenchymatous disease in either lung.

The blood picture showed no notable abnormality. White blood cells 6,000 with 65% polymorphonuclears. Sedimentation rate 33 mm. in one hour. Gastric washings were negative for tubercle bacilli.

The pleural fluid showed a fairly abundant collection of white cells, chiefly mononuclears. A 24-hour culture showed no growth and stained smears were negative for acid fast bacilli. Guinea pig inoculation and culture later showed tubercle bacilli. A diagnosis of left sided pleurisy with effusion, presumably tuberculous, was made and the patient was placed on a strict sanatorium regimen. His further course in hospital is interesting.

On admission, only 50 c.c. of fluid had been obtained from the chest and two subsequent attempts at aspiration proved unsuccessful. Serial x-rays continued to show a fairly dense shadow at the left base which did not diminish in size or density as rapidly as one would expect with normal resolution of pleural thickening and absorption of fluid. Meanwhile the patient's progress seemed satisfactory. On November 22, he weighed 197 lb. and his sedimentation rate had fallen to 4 mm.

About December 3, there developed what at first appeared to be an acute influenzal infection, with a sharp elevation of temperature, (103°), general malaise, etc. The white count at this time was within normal limits and sedimentation rate was 8 mm. The base of the left chest was again explored with a large bore needle but no fluid could be obtained. Temperature continued to range between 100 and 103° and was uninfluenced by penicillin or sulfonamide therapy. X-ray showed no unfavourable change.

On December 24, x-ray showed the development of diffuse miliary involvement of both lungs and by December 31, the patient was acutely ill, complaining of anorexia, headache, drowsiness and a persistent cough. His temperature was now 103° and pulse between 128 and 136.

Treatment with streptomycin was instituted on December 31. He was given 3 gm. a day for the first two days and this was followed by a maintenance dose of 2 gm. a day. The drug was given by intramuscular injection every four hours. During the first week of treatment the patient showed symptomatic improvement as the pulse rate and temperature began to decline. On January 8, the maximum temperature was 101° and the patient was considerably less toxic. He was able to eat three meals a day and his cough was much improved. However, a progress note on February 5, 1947 read as follows:

"Since January 15, the temperature has shown no further reduction. It still reaches an occasional 101°. There has been no further improvement in his cough and his appetite has begun to fail somewhat. Occasional night sweats are readily controlled by atropine. On questioning, the patient complains of some aching in calves of his legs towards night time but he has no other disturbances. There are no headaches and no visual or auditory complaints. His weight which was 197 lb. before the onset of miliary disease and 180 lb. at the commencement of streptomycin therapy is now 164 lb. Weekly blood counts and urinalyses show no change. Sedimentation rate is 31 mm. Chest x-ray shows no obvious change. The impression is gained that while streptomycin is definitely retarding the progression

of this man's disease, he is nevertheless slowly losing ground.''

By February 21, the picture had changed somewhat. Only once in the preceding 2 weeks had the temperature exceeded 99.2° and the patient now showed a definite improvement. His appetite had slowly returned and his cough had almost disappeared. Chest examination disclosed no adventitious sounds. The hæmogram showed no obvious changes. X-ray examination however, showed a definite clearing of the miliary shadows for the first time. In the next few weeks the patient continued to make favourable progress and his weight gradually increased.

At the time of writing (May 2) the patient weighs 186 lb. and his temperature never exceeds 99°. Most of the time he is afebrile. He is up to the bathroom 2 or 3 times a day and his strength is improving with increased exercise. Blood and urine are still normal. Sedimentation rate has fallen to 4 mm. The chest film shows an apparent complete clearing of the miliary shadows and except for some slight pleural changes at the left base it would pass for a normal chest if seen for the first time.

There are still no complaints of headache, vertigo, visual disturbances, etc., although the patient continues to take 2 gm. of streptomycin a day.

SUBSEQUENT HISTORY

Streptomycin was discontinued May 28, 1947, following a total dosage of 301 grams. On June 3 he weighed 191 lb., a gain of 27 lb. since March 6, 1947. His only symptom at that time was a fairly persistent elevation of temperature—99 to 99 1/5°. He continued unchanged until about June 15 when he began to complain of frontal headache which persisted with loss of appetite. Lumbar puncture showed a clear fluid, under increased pressure, cell count 86 per cubic mm. Pandy 3 plus. He was transferred to Gravenhurst Sanatorium June 27 in order to be near his people and died of tuberculous meningitis a short time after his arrival there.

We feel that the lesson to be learnt from this case is that every case of miliary tuberculosis treated with streptomycin should receive the drug intrathecally as well as intramuscularly.

HEPATORENAL SYNDROME WITH RECOVERY

A. F. Perl, M.D.

Provost, Alta.

A report of a case of hepatorenal syndrome seems to be indicated, as, on the one hand ''the concept of possible hepatic or hepatorenal failure after surgery is still doubted by some surgeons, chiefly, as certain writers rather bitterly point out, by those who never have experienced the disaster'' (M. Steiner); while on the other hand, some observers have stated that the condition is more common than references in the literature seem to indicate.

Mrs. J.S., a white housewife of 44 years was admitted to St. Joseph's Hospital, Macklin, Sask., service of Dr. F. L. Eid, on November 4, 1946. She had had her first attack of biliary colic about 8 years previous to admission; at that time she was jaundiced. Two more episodes of biliary attacks followed in the two subsequent years, without jaundice. In the last few years there was fat intolerance, severe epigastric pain radiating to the back, vomiting, and dull aching between the shoulder blades. The family history was irrelevant. Past history revealed two normal pregnancies, and a thyroidectomy and appendectomy 10 and 15 years ago respectively.

Physical examination: alert, well nourished woman, no evidence of jaundice on skin and mucous membranes. A thyroidectomy and appendectomy scar are present. Heart and lungs, electrocardiogram and routine urine analysis normal; blood pressure 120/70.

The patient was put on a high carbohydrate diet, vitamin K and calcium lactate were administered. On the morning of November 7 the patient was operated upon by Dr. Eid. After routine preparation anæsthesia was started with evipal intravenously and continued with ether by the open mask method.

At operation the gallbladder appeared as a solid mass about 2 x 4 cm., embedded in pericholecystitic adhesions. Its thickened and indurated wall was tightly contracted about one large and several small stones. Gallbladder, common and cystic ducts were all embedded in fibrotic tough scar tissue; so that the normal anatomy was largely obliterated. Considerable time had to be spent in sharp and blunt dissection. After ablation of the gallbladder and retrograde probing of common and hepatic ducts, a thin rubber catheter was inserted in the stump of the cystic duct and led through the abdominal incision. Duration of the operation was 80 minutes, most of which was taken up by the necessary dissection of scar tissue. Patient left the operating room in good condition, pulse rate 100, regular, and of good quality.

The pathological report revealed a fibrous gallbladder whose mucous membrane appeared to be completely replaced by fibrous tissue; only occasional small areas of mucous membrane were encountered on microscopical examination.

Postoperative course.—On November 8, at 8 a.m., a small amount of greenish-brown bile discharged from the common duct drain. Temperature 99.8°, pulse 110. At 12 noon temperature and pulse unchanged, intravenous saline started; 5.30 p.m. severe chill, temperature 102°, pulse 140; 6.50 p.m. pulse rate 150; 6 ℥ of dark urine voided, albumen ++. Fair amount of grayish biliary discharge from tube. November 9, 7.30 a.m., evacuation of brownish-grey stool of very foul odour; 12 noon yellowish-green bile discharged from drainage. Catheterization of the bladder yields 25 ℥ of deep brown urine, albumen ++++. Sediment contains some bile coloured casts and leucocytes. Pulse and temperature unchanged.

By 7 p.m. the patient was seen in consultation. Her condition had enormously deteriorated; she was restless, semi-conscious. Pulse 164, blood pressure 58/0, shallow and rapid respirations, skin cold and clammy, venous collapse. She had several involuntary bowel evacuations, greyish-brown of colour and extremely foul smelling. Obviously the patient offered the clinical picture of severe shock. An electrocardiogram revealed a tachycardia of supraventricular origin, and as there was in comparison with the preoperatively taken tracing a slight change in the configuration of the P-waves and the duration of the P-R interval, an auricular tachycardia of toxic origin was also taken into consideration. Carbochol was given intravenously, but without result. The patient's condition kept on deteriorating rapidly, and as the picture of shock was dominant, plasma was given intravenously, and oxygen by nasal catheter, also large doses of penicillin—50,000 U o.h. 2—were administered.

After absorption of 1,500 c.c. of plasma the patient made a spectacular recovery; her pulse rate dropped to 120 initially, and got stabilized around 90 on the evening of the 11th. Her urine contained 120 mgm. % albumen

on the 11th, 40 mgm. % on the 12th, and remained free of albumen and bilirubin starting with the 13th.

On November 20, the patient developed a right pleural effusion which was aspirated and yielded 450 c.c. of a clear fluid, sterile on culture. Apart from this the recovery was uneventful. The patient was discharged on December 15. There was at the time of discharge a small fistulous opening at the original site of the drainage tube, which opening subsequently closed spontaneously. The patient felt entirely well in further follow-ups.

Heyd who described the hepatorenal syndrome first in 1923 distinguishes in a later paper (1942) the following three groups of postoperative liver deaths.

1. Liver death associated with hyperpyrexia and coma. Death ensues in 18 to 36 hours, the patient usually does not emerge from the anæsthesia.

2. Death associated with steadily diminishing jaundice and stupor and coma. After a variable period of from one to seven days the patient develops stupor and oliguria, and dies in coma with hyperpyrexia.

3. Liver death with secondary renal degeneration of severe degree—the hepatorenal syndrome proper. Patients in this group lack hyperpyrexia, and stupor passing into coma. After 48 hours distinct vasomotor collapse ensues with increasing degree of oliguria and marked elevation of non-protein nitrogen. Anuria finally dominates the clinical picture and leads to death.

This syndrome has been observed not only in relation to disease or injury of the liver and biliary tract, but also associated with a great number of conditions originating outside the hepato-biliary system. It has been emphasized in the literature that this syndrome is almost always associated with cholelithiasis when it arises after biliary tract surgery on non-jaundiced patients; most of the patients are over 40, obese, and are satisfactory operative risks; operation, as in our case, is undertaken with no trepidation. In one series of 557 unselected cases of cholecystitis there were 8 liver deaths, mortality rate of 1.4%.

Shock is the one denominator common to many of these cases, regardless whether the disorder arises abruptly, or whether the onset is more insidious, as Herbut points out, and the clinical picture of shock was very dominant in our case. Although blood chemistry readings were unfortunately not obtainable the diagnosis of hepatorenal syndrome was substantiated by the course of events, the clinical picture and the urinary findings. Plasma was administered to the patient primarily to combat the shock, however, according to Heyd, an insufficient amount of protein in the liver may be one of the contributory factors towards establishment of a hepatorenal syndrome, and it is safe to assume that administration of plasma would correct this protein deficiency. There is also a curious and as yet unexplained relationship between vitamin K and liver function. Giving an adequate dose of vitamin K before operation not only prevents bleeding, but also helps the other functions of the liver.

In infectious diseases of the external biliary apparatus the liver is called upon to exercise a detoxifying and bacteriolytic function, a varying degree of liver damage ensues if the ratio of toxic agent to liver function is disturbed to the disadvantage to the liver. Several investigators have been able to produce a picture of hepatorenal syndrome in experimental animals by injection of extract of damaged liver. Draining of the fossa of the gallbladder following cholecystectomy not only provides exit for bile that may have leaked out, but also serves the important function of preventing the accumulation of possibly toxic tissue fluid. It is to be believed that the administration of vitamin K preoperatively, and the establishment of drainage have contributed to militate against liver damage stemming from a very badly infected biliary tract, some dietary restrictions, operative trauma and anæsthesia. Wilensky draws attention to the deleterious influence of high temperature, for instance the excessive heat during the summer months, on the postoperative mortality, especially after biliary tract surgery. We believe that the sharp rise in temperature which occurred on the afternoon of November 8—apparently due to pyrogenic contamination in the intravenous tubing—acted as a trigger mechanism which gave origin to or at least precipitated the succeeding alarming sequence of events.

While it has been stated that not every hepatorenal syndrome terminates necessarily with death, the clinical picture offered by our case was a very serious one indeed; the patient was for all practical purposes moribund in the late evening hours of November 9. We ascribe the remarkable recovery firstly to the administration of plasma, while the large doses of penicillin may have been of help in the heavily infected biliary tree; the rôle of vitamin K and

external biliary drainage has already been discussed.

This patient was under the care of Dr. F. L. Eid of Macklin, Saskatchewan, who performed the operation, and was wholly in charge of the pre- and post-operative management of this case. My sincerest acknowledgment goes to him not only for giving me his permission to publish his case, but also for supplying a very comprehensive and detailed case history.

BIBLIOGRAPHY

1. HELWIG, F. C. AND SCHULTZ, C. B.: *Surg., Gyn. & Obst.*, 4: 1932, 1932.
2. WILENSKY, A. O.: *Arch. Surg.*, 38: 625, 1939. (Very comprehensive bibliography.)
3. LIGHTMAN, S. S. AND SOHVAL, A. R.: *Am. J. Digest. Dis. & Nutr.*, 4: 26, 1938.
4. HERBUT, P. A.: *Ann. Int. Med.*, 25: 648, 1946.
5. HEYD, C. G.: *Am. J. Digest. Dis.*, 9: 348, 1942.
6. STEINER, M.: *Am. J. Obst. & Gyn.*, 51: 678, 1946.
7. BARCLAY, J. A. AND COOKE, W. T.: *The Lancet*, 249: 458, 1945.

CLINICAL and LABORATORY NOTES

REMOVAL OF SENILE WARTS

Daniel McLellan, M.D.

Vancouver, B.C.

The following is suggested as a simple method of removing senile warts. This treatment was discovered by sheer accident. An aged gentleman consulted me with a fractured rib. He had a profusion of senile warts on chest, abdomen, and back, some as large as a fifty cent piece. I first thought of putting a protecting dressing over each wart, but there were so many of them that I decided to put the (zinc oxide) adhesive right on to them, and trust they would take no harm.

In five weeks' time, when I removed the adhesive, the warts were stuck to the adhesive and the skin clean. Since then I have used it on several other cases with the same results in every case.

NEWS ITEMS

Alberta

Dr. A. F. Perl has left Provost, Alta., and has joined the Carruthers Clinic at Sarnia, Ont., as an internist.

British Columbia

The epidemic of anterior poliomyelitis, reported in the last issue is still with us. Some 80 cases have been definitely diagnosed and admitted to the Vancouver General Hospital. There have been many acts of generosity by private citizens who have contributed apparatus for use in the treatment of this disease, the most notable being the gift of the Kinsmen of Vancouver, who gave two iron lungs and several hot fomentation machines.

We record several marriages, amongst them the marriage of Dr. T. W. Tysoe, Britannia Beach; Dr. Wm. Leonard Grant, Vancouver; Dr. Wm. R. MacEwan, South Shalalth; Dr. W. H. Sutherland, recently of Revelstoke who has come to Vancouver to practise, and Dr. J. Leonard McMillan, Vancouver.

Dr. J. H. Sturdy has left the Vancouver General Hospital to join the Department of Pathology at the Banting Institute in Toronto.

Dr. L. A. Patten, for a long time physician at Chilliwack, is recovering from a recent illness, all his colleagues rejoice in his recovery.

Dr. A. A. Gordon who has been doing postgraduate work at the Vancouver General Hospital has now joined the Montreal Pathological Institute at McGill University.

The "Sport of Kings" claims much of the time of several B.C. medical men. Among these is Doctor L. H. Appleby, whose "Ososdry" recently won an important race. His well known "Cum Laude", which has become internationally known, suffered a fracture of the leg recently and it is doubtful whether he will run again. Dr. T. R. Whalley of Vancouver is another physician who takes a keen interest in this sport. He has recently added four new Kentucky thoroughbred fillies to his stable.

Dr. B. Berger and Dr. M. Schreiber have established joint medical offices at Port Moody and Port Coquitlam.

The Vancouver General Hospital has recently added two notable members to its staff. Dr. M. Digby Leigh, formerly anæsthetist in Montreal has assumed the position of Director of Anæsthesia, and his coming to Vancouver is a distinct acquisition to the ranks of the profession. Dr. Leigh has a distinguished record as practising anæsthetist and teacher and has written on this subject.

Dr. H. K. Fidler has also joined the staff of the Vancouver General Hospital as Director of the Pathological Laboratory. He also has a distinguished record in pathology and bacteriology and has been engaged in teaching. He has written several important papers.

Sixteen British Columbia candidates were successful in examinations held by the Medical Council of Canada. The examinations were held in Halifax, Montreal, Toronto, Kingston, London (Ontario) and Vancouver.

J. H. MACDERMOT

Manitoba

Dr. P. H. T. Thorlakson has resigned as professor of surgery in the faculty of medicine, University of Manitoba. His successor has not been announced yet.

The tuition fees for the course in medicine in the University of Manitoba have been increased by $102.00. Veterans, however, will not be affected by this increase.

F. A. B. Sheppard, C.I.E., O.B.E., M.B., B.S.(Melbourne), F.R.C.S.(Edin.), late Professor of Surgery, Madras, India, and J. A. B. Hillsman, M.D.(Virginia), M.D.(Man.), Ch.M.(Man.), late R.C.A.M.C., have recently joined the division of surgery at the Winnipeg Clinic, and L. Cherniak, B.Sc., M.D.(Man.), M.R.C.P.(Lond.), late R.A.M.C., has joined the division of internal medicine of the Winnipeg Clinic.

The new surgical wing of Grace Hospital, Winnipeg, built at a cost of $270,000, was formally opened on July 29 by His Honour, R. F. McWilliams, K.C., Lieutenant-Governor of Manitoba. There are seven special surgical rooms, six private rooms and forty-two semi-private beds in the new wing.

Fifty-three cases of anterior poliomyelitis have been reported in Manitoba up to August 1, but there have been only two deaths.

News Items continued on page 312

THE CANADIAN MEDICAL ASSOCIATION

Editorial Offices—3640 University Street, Montreal

(Information regarding contributions and advertising will be found on the second page following the reading material.)

EDITORIAL

CONFERENCE ON PREPAID MEDICAL CARE PLANS

IN October last our Association, through its Committee on Medical Economics, arranged for a conference on the subject of prepaid medical care plans. This conference which was held in Winnipeg in June of this year, was attended by representatives from six of the largest and best established of these Plans, as well as members of the Medical Economics Committee, with various officers of the Association. The prepayment bodies had in common the following points: (1) they were organized by or with the aid of organized medical groups; (2) they operated on a "non-profit" basis. In all cases they had been evolved for one main purpose, namely to aid the public in meeting the rising costs of medical care.

The reason for the conference was that the Committee on Economics felt that extremely valuable information might be gained for its own studies of the general problem of health insurance by discussion of the work of the prepayment organizations. The aim of the Committee is to keep the Association informed on the subject of health insurance, and to present suggestions for dealing with it. Our stand has always been that we approve of the principle of Health Insurance but in its operation the best type of service must be rendered, and our professional rights protected, although no concrete plan has ever been suggested by us. It was felt that much could be learnt from the experience of those who for years have carried on the type of work which has many features of what a health insurance scheme must include.

Since health insurance would be Dominion wide the possibility of a Dominion charter being obtained for a given Prepayment Plan was discussed. The advantages would be that members would be equally protected in any Province they might be in; certain large employers such as the railways would be inclined to help a national rather than a local body; the civil service, which is probably the largest single group of workers in the country, would be covered. On the other hand, it was thought by some that no one plan would be satisfactory across the country. Local conditions vary too much; and if there were a variety of plans rates would differ, and fees and coverage would be different.

It might be possible to overcome some of these difficulties by setting up a Dominion organization which would act as a collecting and distributing body for each provincial group.

The discussion on these points was crystallized in a decision to request our Association to set up a committee to consider the advisability of forming a federal organization to extend the purposes of the existing prepayment plans. This committee would include representation from each of the six Plans attending the Conference. It was realized that all this work was exploratory only, but if any Dominion-wide plan for prepayment was ever to be considered it was imperative that close and continuous study of all its aspects be carried on. The value of this work would be very high not only in itself, but in its evidence of the active concern of our profession in trying to evolve a plan which could be utilized in any future government policy.

Many other points were discussed, and recommendations made: *e.g.* in the establishment of any voluntary prepaid medical service plan endorsed by the medical profession, the organization should be set up under joint lay and medical control, so that at all times the control of matters concerned with the purely professional side of the plan would be determined by the medical members.

On the subject of payment of specialists under any given plan it was

recommended that practitioners who had been recognized as specialists by the Royal College of Physicians and Surgeons of Canada be paid at specialist rates for work done in their special fields, and that remuneration at general practitioner rates be paid for all other work done by them under the Plan.

Another recommendation was to the effect that in all areas in which a public demand exists sound medical care plans endorsed by the medical profession should be adopted.

It must be repeated that prepayment plans are not regarded as the complete solution of the problem of health insurance. They have definite limitations. But they serve to focus attention on one very vital element, the economic. They are therefore a valuable starting point from which to develop any wider scheme of medical care.

CENTENARY OF THE COLLEGE OF PHYSICIANS AND SURGEONS OF THE PROVINCE OF QUEBEC

WE desire to extend to the College of Physicians and Surgeons of the Province of Quebec our hearty congratulations and best wishes on the occasion of the centenary of the College, to be celebrated on the 10th and 11th of this month in Montreal. We understand that a fitting program has been arranged for the occasion with suitable ceremonies both religious, scientific and historical. The City of Montreal is formally welcoming the members of the College, and the fact is recalled that no less than four medical men have at various times in the past been elected as mayor of Montreal.

The history of the College shows that throughout its development it has steadily maintained high ideals and standards of practice in medicine. We wish it continued vigour and prosperity.

EDITORIAL COMMENTS

The Nomenclature of Hæmatology

There is much confusion in hæmatological nomenclature. This is so prevalent that it is difficult to interpret a differential cell count on blood or bone marrow from one laboratory or even from different technicians of the same laboratory without personally visiting the laboratory and learning of the criteria of cell identification and disease classification in use there.

A cell may receive as many as twelve different labels, and sometimes the same name is used for different cells. The same confusion applies to hæmatological diseases, the leukæmias receiving various classifications in the different clinics. Trained hæmatologists usually have not much difficulty in recognizing the given cell or disease from the terminology used, as they know the literature and at least some of the clinics. But to the average practitioner, clinical pathologist or even internist the confusion is very real. The difficulty is that each author has developed his own terminology without describing easily recognized lines of demarcation.

A timely suggestion to remedy the situation has been made by Dr. Edwin E. Osgood, of the University of Oregon Medical School. Dr. Osgood feels that a carefully selected Committee should be appointed during the week before the meeting of the American Society of Clinical Pathologists in Chicago, October 28 to 30, 1947, "to make recommendations to that body as to the preferred name and the criteria of differentiation for the cells and diseases of the blood and blood-forming organs".

Apparently some may criticize any attempt to standardize a nomenclature which has not yet quite found its feet. But this could be remedied by having such a committee revise the terms at regular intervals. In general, the standardization of terms tends to help in the diffusion of knowledge.

Excerpta Medica

Abstracts from the medical journals of the day form an essential part of medical literature. One of the most recent ventures of this kind is *Excerpta Medica,* published in Amsterdam. This provides abstracts in English of practically all the medical literature of the day. These appear in sectional journals each dealing with a seperate branch of medicine and the basic sciences. The latest of these to appear is that on Radiology. There will be 15 volumes altogether.

This ambitious scheme calls for a very large staff of abstractors and editors all over the world. Judging by the abstracts which have so far appeared the work seems to be admirably done, and with the completion of all the volumes, which will all be indexed, a very valuable survey of contemporary literature will be available.

Symposium on Cancer

We would draw attention to the notice appearing on page xxxvii regarding the two-day symposium on cancer in Toronto on October 21 and 22. A group of outstanding speakers have been secured for the occasion including Sir Henry Dale of London, England, and Dr. D. W. Cowdry of St. Louis, Missouri. The meeting will be held in the auditorium of the Sunnybrook Hospital in Toronto, and it is expected that many physicians will take advantage of it.

MEN and BOOKS

A HISTORIC MEDICINE CHEST

Richard J. Cyriax, M.R.C.S., L.R.C.P., D.P.H.

Leamington Spa, Eng.

Captain Sir John Franklin, commanding H.M. ships *Erebus* and *Terror*, sailed from the Thames in May, 1845 to seek a North-West Passage. The two ships, after having been beset for about nineteen months in the ice of Victoria Strait, were abandoned on April 22, 1848 by Captain F. R. M. Crozier, on whom the command had devolved after Franklin's death in June, 1847. Crozier and 104 officers and men landed at Point Victory, King William Island, and then tried to reach the Hudson's Bay Company posts in Northern Canada by way of the Great Fish River. He and his entire command perished, and their fate was not definitely ascertained until the expedition, led by Captain (subsequently Admiral Sir) Francis Leopold McClintock, searched King William Island in 1859, eleven years after the disaster.

Lieutenant Hobson, the second in command of this expedition, reached Point Victory before McClintock himself, and found there the medicine chest now to be described. There can be no reasonable doubt that this chest, which contained medicines and surgical sundries, was left at Point Victory after Crozier had abandoned his ships but before he started for the Great Fish River. It lay among a large quantity of discarded equipment which his officers and men had left strewn around the cairn in which was deposited the last written message which has reached the civilized world from the Franklin expedition. Since McClintock's narrative does not specify the position occupied by the chest itself when it was found, whether this position was such as to favour leakage or evaporation of the liquid medicines cannot be ascertained, but the lid must have been closed, for the contents of the chest were remarkably well preserved in spite of having been exposed for eleven years to a Polar climate. The chest was not touched by Eskimos before it was found by Hobson, and it bears no obvious signs of having been injured by wild animals. It is now preserved in the National Maritime Museum at Greenwich. McClintock's published narrative includes an inventory of the chest's contents,[1] but no detailed description, so far as the writer is aware, has hitherto appeared in print.

The chest itself, which is made of mahogany and fitted with a lock and strap, now broken, measures 14 in. by 13 in., and has a depth of slightly more than 5 in. It was originally covered with canvas, fastened to the wood by tacks, but the canvas is no longer complete, portions having apparently rotted away. The chest is fitted with a wooden rack for holding medicine bottles, and also with a smaller rack, now loose. A thin pad, made of plush or some similar material, is fixed to the inside of the lid and is so placed as to lie above the bottles when the chest is closed. A sheet of paper, on which is written in ink a list of the chest's contents, is attached to the lid above the pad, but unfortunately most of the writing is too defaced, evidently by damp, to be legible; the names of only some of the medicines can still be seen clearly. The chest bears no visible Government or manufacturer's mark, but three lines resembling writing in ink appear on one side of the canvas cover. This writing is so smudged and defaced that only two letters are distinct—"ML", placed a short distance in front of the second line. These letters may be some person's initials, but if so are not those of any of the four Medical Officers (S. S. Stanley, H. D. S. Goodsir, J. S. Peddie, A. Macdonald) or of any other member of the Franklin expedition.

The chest contains twenty-three medicine bottles, all of which, with the one exception noted below, are made of clear glass, and are fitted with glass stoppers and leather caps, fastened to the necks of the bottles with brown thread. All the bottles, except two, are labelled, and the writing, done in ink, is perfectly legible on every label. McClintock's enumeration, published eighty-eight years ago, mentions the amount of drug still left in each bottle when the chest was found, and his account has been retained for reasons that will appear later. His description is, however, no longer strictly accurate, especially as regards the liquid preparations, for some of these have undergone slight loss, presumably owing to evaporation.

The bottles numbered one to fifteen inclusive in the list that follows are all of the same shape and size; each has a capacity of about two fluid ounces. One of these bottles, now empty, was found to weigh, with stopper and leather cap, nearly 2 oz. 7 dr. apothecaries' weight. This determination provides an approximate estimate of the quantities of solid drugs contained in the other bottles of similar size, for these bottles must all be of about the same weight.

1. One quite clean empty bottle. This is evidently the one which, according to McClintock,

was empty when found, and was labelled "Spirit Rect." The label is missing.

2. "Ipecac. R. Pulv", full. It contains about 10 dr.

3. "Ol. Olive", full. It contains about 2 fl. oz.

4. "Mur. Hyd.", seven-eighths full. It contains about 3 oz. 4 dr. of a heavy white crystalline powder, no doubt perchloride of mercury. This bottle would have contained about 4 oz. when full, and was probably incompletely filled when taken from the ships. One hundred years ago corrosive sublimate was used principally for internal administration, but it could not have been safely dispensed as a medicine without accurate weighing; and scales and weights were not in the chest when this was found, though they may have been included in the original equipment and have been removed before the chest was discarded. The drug was sometimes used in lotions or as an escharotic, but it is difficult to imagine any condition or conditions for the treatment of which half an ounce can have been required during the few days that elapsed between Crozier's abandonment of his ships and his arrival at Point Victory.

5. "Ipecac. P. Co.," full. It contains about 2 oz.

6. "Tinct. Opii Camph." It was three-quarters full when found and then contained about 12 fl. dr.

7. and 8. Two bottles labelled "Tinct. Tolut". Each was one-quarter full when found and then contained about 4 fl. dr.

9. "Vin. Sem. Colch.", full. It contains about 2 fl. oz.

10. "Vin. Sem. Colch.", one-quarter full when found, and then containing about 4 fl. dr.

11. "Scammon. Pulv.", full, contained about 7 dr.

12. "Jalap R. Pulv.", full, containing about 8 dr.

13. "Zingib. R. Pulv.", containing about 7 dr.

14. "Liq. Ammon. Fort.", three-quarters full when found and then containing about 12 fl. dr.

15. "Submur. Hyd.", broken, empty. Since this bottle, according to McClintock, was broken but full when found, Hobson probably threw away the calomel at once in order to avoid its being shaken all over the inside of the chest during his subsequent sledge journey. Some white powder still adheres to the pieces of broken glass.

The four bottles next to be described are much smaller than those enumerated above. Each has a capacity of about 4 fl. dr.

16. "Ol. Caryoph." It was one-fifth full when found and then contained slightly less than 1 fl. dr.

17. "Ol. Menth. Pip.", empty.

18. "Quinine Disulph.", empty. Since no drug remains in the bottle, whether it was powdered or crystalline cannot be determined. If the former, about 200 gr. would have filled the bottle if the quinine sulphate had been poured in loosely and not pressed down.

19. "Hydrarg. Nit. Oxyd.", (red precipitate), full.

The following three bottles are much larger than any of those described above. Each has a capacity of about 4 fl. oz.

20. "Pulv. Greg.", full, broken. It was broken when found. A piece of lint has been tied round the bottle, presumably to keep the pieces together, but some of the powder has escaped, with the result that the chest and its contents smell strongly of rhubarb.

21. "Magnes. Carb.", full.

22. "Camphor", full.

23. An unlabelled poison bottle which, when found, was three-quarters full. It contains a dark fluid, and is evidently the one described by McClintock as unlabelled and as containing Tr. Opii. It differs from all the other bottles in four respects: it is corked and not stoppered, has no leather cap, is made of dark green glass, and is stamped with a device which includes a foul anchor and is possibly the mark used by the Society of Apothecaries of London to identify the pharmaceutical products supplied by it to the Navy. This bottle has a capacity of about 4 fl. oz., and contained about 3 fl. oz. when found.

The remaining contents of the chest are as follows: (1) a pewter syringe, 4 in. long. It is perfectly clean and shows no sign of use. (2) a circular metal box said on a label to contain ground ginger but actually containing what seems to be an ointment, now dried up almost into a ball. McClintock's inventory mentions a box containing shrunk ointment, and no other article in the chest agrees with his description. The ointment is of a light yellow colour and possesses no definite odour; it may be "unguentum resinæ", which was very often used in surgical practice. (3) Three very small test tubes, each 2 in. long. They are all the same size, have very wide flanges, and show no signs of use. (4) A sealed metal box, the contents of which rattle. This is doubtless the box containing pills, which McClintock thought were purgative. (5) A metal canister, 10 in. long, 2½ in. in diameter. It contains a large roll of light yellow adhesive plaster. (6) One probang. A sponge, the size of a cherry, is fixed to the thin end of the tapering handle, which is about one foot long, and made apparently of whalebone. The sponge is not stained. (7) Oil silk, with a little cotton-wool, probably used as wrapping. The oil silk appears to be a large piece which has been folded several times, the opposing surfaces having become firmly adherent. (8) Two 2½ in. roller bandages, tied with thread. (9) A very long double-headed roller bandage, 5 in. broad. (10) Many pieces of lint, large and small, some folded. The lint is very soft and of extremely good quality. Some of the smaller pieces may have been used as packing material. (11) Some thin leather,

apparently for capping the bottles. (12) A small quill pen, stained with ink. (13) One unsharpened lead pencil. (14) A farthing dated 1839.

Neither the chest itself nor any article in it, excepting only the bottle of Tr. Opii, bears either a Government mark or any other indication of having been supplied through official channels, so that a question which arises is whether the chest was Government or private property. The second of these alternatives is suggested by the mixed nomenclature used on the labels of the medicine bottles. Three pharmacopœias (London, Edinburgh and Dublin) were then current in the United Kingdom; some of the names on the labels follow the London, others the Edinburgh pharmacopœia, others again (*e.g.*, "Mur. Hyd.") were unofficial. Moreover, the chest itself and its fittings do not seem to be constructed sufficiently strongly to withstand the rough usage to which they might have been subjected under the service conditions. The regulations in force regarding medical equipments in the Navy when the Franklin expedition sailed, described in detail four standard equipments that varied in size in accordance with the number of men for whom they were intended, but the smallest size mentioned was designed for forty men for one year.[2] A still smaller equipment, such as that contained in the chest left behind at Point Victory, does not appear to have been the subject of official regulations, which consequently shed no light on the question at issue. Since consideration of the chest's contents shows beyond doubt that they were intended to be used only by a Medical Officer, their owner, if they were private property, must have been one of the Surgeons or Assistant Surgeons.

The equipment, as Hobson found it, included none of the instruments (*e.g.*, lancets, scissors, needles) such as are required for the simplest surgical procedures, though it did include bandages, lint, a syringe and a probang. The chest is unlikely to have been intended merely as a supplement to other equipments; it was probably taken for use only during the march from the ships to Point Victory. Hence some of its contents may have been abstracted before it was discarded and have been added to the much more comprehensive equipments that must have been kept. In addition to surgical sundries, the articles removed may have included a set of scales and weights and a graduated glass, but all the patients were adult males for whom the Medical Officers could have dispensed, accurately enough, the solid drugs (except corrosive sublimate) by mere inspection, the liquids by the the drop method.

Even if the chest was private property no useful purpose would have been served by taking empty or partially emptied bottles of medicine. Hence every bottle was probably full or nearly full when the march from the ships began. The interesting question then arises whether the drugs that were missing when the chest was found by Hobson shed any light on the disease under treatment. It is necessary first to determine which drugs were probably dispensed, for the absence, partial or complete, of some of them does not necessarily prove actual use.

The chest lay for eleven years at Point Victory. All the liquid preparations, especially the more volatile ones, were subject to loss by evaporation, at least during every summer; and in fact some of them (*e.g.*, Vin. Sem. Colch. and Tr. Tolu) in spite of preservation in a sealed case under museum conditions, have undergone slight diminution in volume since McClintock's narrative was published in 1859. Moreover, nothing can now be ascertained about special conditions which might have influenced the rate of evaporation before the chest was found. Nevertheless, loss by evaporation, though it doubtless did occur, cannot have been the only cause of the empty or partly emptied bottles. First, the chest contained two bottles of Vin. Sem. Colch.; one was and still is full, the other was one-quarter full. Several causes of this can be suggested, but the most probable one seems to be that at least some of the original contents of the partly emptied bottle were dispensed. Secondly, the cork of the unlabelled bottle containing Tr. Opii., and the rim of the bottle itself, are slightly crusted with a dark powder. The question whether this deposit can have been the result of leakage is discussed later; it will suffice to say here that the appearance suggests use, and that even if evaporation did occur, it would have been confined to the water and alcohol in the tincture. Lastly, the bottle labelled "Quinine Disulph." was quite empty when found, and the quinine sulphate itself would not have evaporated.

An inverted or tilted position of the chest itself while it lay at Point Victory would have favoured leakage of the liquid preparations. But such leakage, if indeed it did take place, can scarcely have had any greater effect than that of slightly assisting evaporation by bringing the liquids into direct contact with the bottle stoppers. Had any of the coloured liquids (*e.g.*, Tr. Opii Camph.) escaped in appreciable amounts, they would have stained the leather caps on the bottles and probably some of the other contents of the chest; however, signs of such staining are absent. Moreover, there can be no reasonable doubt that while the chest lay at Point Victory, all the bottles, with the exception of the one containing Tr. Opii, were securely capped. That caps from the empty or partly emptied bottles were found lying loose in the chest and were then replaced by Hobson, seems most improbable. The rough treatment to which the chest must have been subjected during the march from the ships to Point Victory would have rendered firm closure of the bottles by means of the stoppers and caps a paramount necessity. It is difficult to

understand why the bottle of Tr. Opii was left without a cap; perhaps some of the contents were used at the last minute, just as the start was made for the Great Fish River.

The chest must have been subjected every winter to temperatures below that of the freezing point of water, but whether any of the liquid preparations froze is very questionable. Nearly all of them contained alcohol, which would have lowered the freezing point; and none of the bottles containing liquids burst. Moreover, none of the leather caps shows signs of having been stretched or forcibly displaced, so that there is no reason to suppose that any stoppers were forced out of the bottles by freezing of the contents. Some of the pieces of lint are discoloured, but the stains resemble those caused by rust. Water must have percolated into the chest every summer, and could have carried rust from the tacks that fastened the canvas cover.

The facts thus warrant the definite conclusion that, even if adequate allowance is made for loss by evaporation, several drugs were probably used.

It is now necessary to consider the bearing of the circumstances, believed to have prevailed when Crozier abandoned the ships, on the diseases and disabilities likely to have required treatment during the few days that the medical officers had the chest in their possession. According to the record written at Point Victory on April 25, 1848, and deposited in a cairn there, Crozier had abandoned the ships on April 22, and intended to start for the Great Fish River on April 26. There is no proof that he did start on that day, but he can reasonably be presumed to have done so. The medicine chest thus appears to have been kept for not longer than five days after the ships had been abandoned, that is to say from April 22 to April 26, 1848, inclusive.

The physical condition of many of the officers and men during these few days can be inferred without serious error. All the available evidence suggests, as McClintock[3] pointed out, that most of the men were suffering severely from scurvy, and the short time that elapsed before the attempt to reach the Great Fish River became a disaster, shows only too clearly that many were already unfit to travel when they left the ships. Moreover, fifteen miles of very rough ice lay between the ships and Point Victory. The boats and sledges were dragged entirely by manpower and are known to have been both very heavy in themselves and grossly overladen. The physical exertion needed to haul these excessive loads must have been immense, and it was doubtless the resulting exhaustion that led to the wholesale abandonment of equipment at Point Victory. Adequate reasons thus exist for concluding that scurvy, complicated by the diseases caused by severe exposure in a Polar climate, would have called for medical attention during the march from the ships to Point Victory.

On the assumption that every bottle (except the one containing corrosive sublimate) was full when taken from the ships, the following list, based on McClintock's inventory and the details given above, shows the approximate quantity of every preparation that may have been used before the chest was discarded. The doses advised by different authors a century ago were not uniform but those mentioned below were the usual ones.

1. "Spirit Rect.", nearly 2 fl. oz. Whether any spirit was used must remain an open question, for all of it may have evaporated before the chest was found.

2. "Tinct. Opii Camph.", about 4 fl. dr. The name suggests that this tincture was prepared according to the Edinburgh formula. If so, the strength was 1 gr. of opium in 4 fl. dr., and the dose was 1 to 3 fl. dr. The corresponding London preparation, "Tr. Camph. Co.", contained slightly less opium but the dose was the same.

3. "Tinct. Tolut.", about 22 fl. dr. The name suggests the Edinburgh preparation, the strength of which was approximately one part of Balsam of Tolu in eleven parts of rectified spirit, and the dose 1 to 2 fl. dr. The London preparation, "Tr. Balsam Tolut.", was weaker, but the dose was the same. A good deal of the alcohol may have evaporated before the chest was found.

4. "Vin. Sem. Colch.", about 11 fl. dr. The strength was 1 in 5 of sherry, and the dose ½ to 2 fl. dr. This wine was not official, but many physicians preferred it and other preparations made from colchicum seeds to those made from the corm.

5. "Liq. Ammon. Fort.", about 4 fl. dr. This was used externally as an epispastic, but never internally without dilution. One part, mixed with two parts of water, produced the "Liquor Ammoniæ" of the London Pharmacopœia, and the dose of this dilute solution, which contained about 8% of ammonia, was 10 to 30 min. usually administered in a large glass of water or milk. This was used principally as a stimulant in such conditions as syncope, and sometimes for hyperacidity. As is mentioned below, it may possibly have been employed as a solvent for quinine sulphate.

6. "Ol. Caryoph.", nearly 3 fl. dr. The dose was 2 to 8 min. This volatile oil, apart from its use as a flavouring agent, was prescribed principally as an antispasmodic and aromatic stimulant.

7. "Ol. Menth. Pip.", about 4 fl. dr. The dose was 2 to 5 min., usually dropped on sugar. It was used for the same purpose as oleum caryophylli.

8. "Quinine Disulph." For reasons already given, the quantity originally contained in the bottle cannot be estimated exactly, but is un-

likely to have exceeded 200 gr. The dosage recommended varied within very wide limits in accordance with the purpose for which the drug was used; the usual dose for an adult was 1 to 5 gr., but much larger doses were prescribed in cases of malaria and of "acute rheumatism". The drug was probably given in the form of powder during the march from the ships to Point Victory, for the chest contained no mineral acid to act as a solvent. A preparation resembling Tr. Quinin. Ammon. could, however, have been made by dissolving the quinine sulphate in the rectified spirit and solution of ammonia included in the outfit.

9. "Tr. Opii" (in the unlabelled poison bottle), about 4 fl. dr. The London preparation was made by macerating 3 oz. of opium in two pints of proof spirit, and the dose was 10 to 30 min. The Edinburgh preparation was of much the same strength, but was made with rectified spirit and water.

Medical opinion was somewhat divided on the subject of the control of scurvy by drugs; the one usually recommended was citric acid, and some authorities advised potassium nitrate. But these drugs, if prescribed at all, played a subsidiary part in the treatment, which consisted when possible principally of hygienic and dietetic measures. Fresh food was always given when it was procurable. Under the special conditions of Arctic service, lemon-juice was the standard preventive and remedy, and the Franklin expedition was supplied with 9,554 lb., which was sufficient to supply every officer and man for about three years and two months with 1 oz. a day, the usual allowance in the Arctic.

Neither citric acid nor potassium nitrate was included in the chest's contents. But the chest itself could not have contained in addition to its present contents, more than very small quantities of citric acid and potassium nitrate, and these quantities would have been quite inadequate for prolonged treatment of many cases of scurvy. Moreover, even if these drugs were taken and were not wholly exhausted when the chest was discarded, the quantities still remaining, no matter how small, would undoubtedly have been retained if scurvy had become widespread. The contents of the chest thus throw no light on the prevalence or not of scurvy, but they certainly furnish no grounds for questioning the accuracy of McClintock's opinion that most of the officers and men were severely affected.

As regards other diseases, several are suggested by the drugs that seem to have been used. Tr. Camph. Co. and Tr. Tolu. were, as they still are, common ingredients of cough mixtures, and tolu seems seldom, if ever, to have been prescribed except as an expectorant. Diseases associated with cough, such as bronchitis, may therefore be reasonably presumed to have occurred. Colchicum was a recognized remedy for gout, gouty conditions, and an ill-defined group of disorders termed "rheumatism". Gout may but is not likely to have attacked men who had lived for nearly three years in the Arctic on a diet which, even if adequate, can hardly have been luxurious, so that the disease requiring the administration of colchicum was probably "rheumatism" rather than gout. Moreover, the occurrence of bronchitis and fibrositis would have been favoured by the sudden change from the comparatively sheltered conditions obtaining in the ships to the very severe exposure encountered during the march to Point Victory.

Tr. Opii. apart from its obvious uses, was one of the two standard remedies (the other was Vinum opii) for snow-blindness. It was applied locally to the eye, which was then covered. Snow-blindness occurred so often among Arctic explorers that Crozier's officers and men are very unlikely to have escaped entirely in spite of the wire gauze goggles which they wore as preventives. Another disorder for which an opiate was the usual remedy was diarrhœa, which not infrequently attacked members of sledge parties.

Cases of frost-bite must have been frequent. The affected part was at once either subjected to gentle friction with snow, or if possible immersed in cold water. The after treatment frequently included the use of so-called "anodyne cataplasms" or "anodyne applications", which probably contained some preparation of opium, but I have failed to find in the older literature an exact account of their composition. Resin ointment containing a small amount of red mercuric oxide seems to have been used occasionally if superficial sloughs formed, and a bottle of this oxide was taken.

Volatile oils, rectified spirit and ammonia may have been prescribed for physical exhaustion and its consequences. The usual stimulant would have been rum. But the expedition, which had been in the Arctic for two years and nine months, had been supplied with enough spirits to last only two years and five months; thus though nearly one-fifth of the officers and men who had sailed from England were dead when the record was written at Point Victory on April 25, 1848, the supply of rum, if not wholly exhausted, had in all probability fallen to an extremely low level by then.

Quinine sulphate, apart from its uses as an antipyretic and antiperiodic, was prescribed in so large a number of diseases as to afford no positive indication of the reasons for its administration during the march to Point Victory. If the quinine was used as an antipyretic, it must for some reason have been preferred to Dover's powder, the bottle containing which is full.

None of the surgical instruments show signs of use. The only ointment in the chest was shrunk when found by Hobson, so that whether any had been used is uncertain. The chest con-

tained three other preparations which were no doubt taken for surgical purposes—red mercuric oxide, olive oil, and corrosive sublimate. The first two of these cannot have been used, for the bottles containing them are full; and the third, for reasons already given, is unlikely to have been used.[4]

To sum up: the contents of the chest furnish no confirmation of McClintock's conclusion that scurvy was the principal cause of the final disaster. Conversely, they afford no evidence in the least suggesting that this conclusion, which was based on quite different grounds, was not securely founded. They do, however, show that some of the drugs could have been but were not necessarily used for conditions known from other sources to have been in all probability prevalent. The evidence which the chest affords, slender as it is, thus tends to confirm what was previously known, without adding further proofs.

I am indebted to the Trustees of the National Maritime Museum for their kind permission to inspect the chest and to publish this description.

REFERENCES

1. McCLINTOCK, SIR F. L.: *The Voyage of the "Fox" in the Arctic Seas*, 1st ed., London, 1859.
2. *Regulations and Instructions for the Medical Officers of His Majesty's Fleet*, London, 1835.
3. McCLINTOCK, SIR F. L.: op. cit., 5th ed., London, 1881.
4. The following books have been consulted regarding medical and surgical practice a century ago: R. Hooper, *Lexicon Medicum*, 7th ed., edited by K. Grant, London, 1839. T. Watson, *Lectures on the Principles and Practice of Physic*, London, 1843. J. Elliotson, *The Principles and Practice of Medicine*, London, 1839. A. T. Thomson, *The London Dispensatory*, 9th ed., London, 1837. S. Cooper, *A Dictionary of Practical Surgery*, 7th ed., London, 1838. R. Liston, *Elements of Surgery*, London, 1840.

ASSOCIATION NOTES

VALEDICTORY ADDRESS

Wallace Wilson, M.D.

[*In his valedictory address as retiring President Dr. Wallace Wilson referred first to the profound changes that are occurring in all phases of human affairs in all countries. Canada can in no degree stand apart from such changes and must play her part in world affairs. Dr. Wilson continued:*]

At home, in these days of education, books, newspapers, telephone, telegraph and radio, a formed, united public opinion, be it in municipality, province or nation, has an almost frightening power and influence. As doctors and as an Association, our closest and most intimate interests are primarily concerned with the health of the people. and we should do all we can to mould and direct public opinion along lines that will produce the greatest amount of health amongst the greatest number of people. How best can this be accomplished? In some respects, the Canadian Medical Association stands in much the same relationship to its Divisions as does the Federal Government to the constituent Provinces. Within the Divisions lies much autonomy, and that is as it should be. In each of the Provinces, with its responsibility for health and freedom of action therein, there will arise problems, and governmental decisions will be made that are of importance to the profession of the whole of Canada, but which will, at the same time, be of very particular interest to the profession within that Province and must be largely dealt with by it.

The rôle of our Association in such cases must be one of support, help and guidance where called for. The rôle of the Divisions in dealing with provincial questions must be one in which consideration is given to the over-all picture and should be carried out in conformity with the general policy and principles laid down by the parent body—a policy and principles already subscribed to by all Divisions. In the past, in this regard, there has been no difficulty or the slightest disharmony, nor will there, I am sure, be any in the future. What the Divisions should all continue to remember is that the Canadian Medical Association cannot lay down policy or enunciate principles without the approval of all the Divisions.

The extent, the harmony and spontaneity of the unity within the Association in the past can be emphasized by reminding you that there has been in existence no British North America Act for organized medicine in Canada; no act that lays down and differentiates powers and authority as between the Canadian Medical Association and its Divisions. The existence and strength of our Association are dependent upon its being the unifier, guide and mouthpiece of its nine Divisions; and it is important that when a Division is dealing with its own local provincial problems, it has behind it through the Association the approval and support of the other eight Divisions. Our Association is a delicately poised body held in position by the united support of all the Divisions. So that it be not pushed off balance, it is most necessary that all questions wherein the parent body is to speak and act for organized medicine should be settled and agreed upon by Executive and Council in open and free discussion. At these meetings of the representatives of the Divisions is the place "where issues should be aired, talked out of existence or talked into solution".

As an example of what is meant, let us look back for a moment at the question of publicity, and by publicity, I mean the dissemination of information to the profession and the public; the education of our members and the people in health matters and the public enunciation of the policies and principles to which our Association is committed. For a matter of years, the question of the establishment of a Publicity or Public Relations Office with the administrative framework of our Association has been discussed periodically at both Executive and Council meetings. Two years ago, a step

forward was made in the appointment of Dr. A. E. Archer as part-time Consultant in Medical Economics to the Association. In this field Dr. Archer has done splendid work and, particularly in those Divisions where the profession has been faced with immediate governmental action in the field of health services, his advice and support have been frequently sought and highly valued.

But have we gone far enough? Should a central office provide regular press releases? Should that office be ready at all times to reply to or comment on items appearing in the press and pertaining to the welfare of the public and the profession? Should there always be available in the central office someone trained and qualified to move into a Province and there, with the local profession, meet various lay groups for the purpose of mutual education with reference to the problems of health services? A few years ago, this was done in Toronto by the Nucleus of the Committee on Economics and Dr. Archer with good results. And, finally, should there be Divisional public relations committees, and if so, how are we to tie their policies and activities with those of the central office so that uniformity may be maintained as to publicity concerning our policies and principles? In all this, it can be readily seen that the establishment of such a department means two things; it means that all Divisions must agree as to its necessity and be prepared to meet the very considerable cost involved, and it means that a rather detailed policy must be worked out and supported by the Divisions.

During my trips as President, it gave me great pleasure to see how well the rehabilitation of our armed forces medical personnel was progressing. It appeared that the vast majority of all those seeking further training following discharge had been placed, and in spite of the universal shortage of office space, most of those returned to or starting practice were well on their way to being satisfactorily absorbed into the stream of civilian life. The thanks of the Association are due to all Advisory Committees for the generous and painstaking time given to their counselling services.

At this time, it is necessary to note the important development that is taking place across Canada in the growth of Voluntary Prepaid Medical Service Plans and, most particularly, to note those plans that are or will be under the control or supervision of the medical profession. The four-day conference which was held recently between representatives of plans and members of our Committee on Economics, was of great import and was a success. Much good to the public and the profession will result from such conferences, and it is most necessary that all doctors be aware that the advent and growth of these plans implies a radical change in our methods of providing health services to the people.

These plans are here to stay, grow and expand, unless they commit suicide by being inefficient in administration and careless in the kind and quality of the services provided; or unless they die of starvation as the result of a prolonged major economic depression. In either event, it is quite conceivable that the State might then intervene. The greatest guarantee of permanent success and the strongest incentive to call forth governmental co-operation rather than intervention will derive from the spontaneous, active and intelligent support of all members of the profession. Only with the co-operation of all doctors in an area where a plan is operating can it be run efficiently or can the services rendered be of a high order. Make no mistake about it; wherever a plan is operating, there will the profession be on trial. And so, whenever a majority of the doctors endorses a plan, then all should get behind it, provide the best services they are capable of and so guarantee all success possible within the limits of that plan. More and more we are insisting on our ability to enter into contracts to provide health services. More and more we must demonstrate that our performance justifies our claims—and our performance should not stop at just providing good medical services. We are all perfectly well aware of the fact that you cannot foster and maintain health to the full unless at the same time you also deal with poverty, and housing, faulty nutrition, hours and conditions of labour, leisure, etc. Such a statement, I know, appears rather trite and the correction of the many faults in our social conditions has been given lip service more often than anything else. But in our private practices, in our Association and in these Medical Service Plans, we should lose no opportunity to encourage and co-operate with all agencies striving towards the ideal of full abounding health for all. Protection against the cost of illnesses, yes; more medical services to more people, yes; but these are not in themselves necessarily sufficient to raise and maintain the maximum standard of health.

The question of the status of our general practitioner members has been receiving the earnest consideration of your Executive. It is felt that that status should be more clearly defined and strengthened and more clearly recognized. Aiming at giving him more help in his work, discussions have taken place with reference to the stimulation and encouragement of clinical research amongst general practitioners and also with regard to the certification of general practitioners as such. To study the whole question, your Executive will set up a committee, and it is expected that following study and investigation, this committee will submit definite recommendations from which your Executive can evolve concrete proposals for presentation to Council.

I have said that our Association has responsibilities that extend beyond our national sphere.

What are these international and world responsibilities? Certainly to do everything in our power to support the United Nations Organization in its efforts to preserve universal peace, to support through our government the World Health Organization and, more directly, to lend our active support to the World Medical Association.

To date, your Association, through its General Secretary, has played a not insignificant part in these two world bodies. Should we continue? Within our membership, opinions concerning a United Nations Organization, a World Health Organization and a World Medical Association, probably fall into three groups.

1. Those amongst us who are "neither hot nor cold" and to whom such world organizations appear as interesting possibilities, but far off, impersonal and about which, as individuals or even as an association, we can do little.
2. The "realists", who point to the fate of the League of Nations and are not optimistic concerning the fate of similar organizations in our day, believing rather that we should concentrate on our immediate tasks at home.
3. Those who believe that, as an Association we should, whatever the outcome will be, participate actively in a World Medical Association and support our Government in furthering a World Health Organization, considering both as definite contributions towards world peace and health.

All three groups should consider the alternative. Is it to be Geneva and Paris, or only Chalk River and the testing grounds of New Mexico? Of course, it may be that we are not ready for world organizations and world peace, and that it will take another war to convince us, in which event the people of the world may not be given another chance of world unity for many centuries. Medicine, unhampered by political considerations, can make a very special contribution to peace and health, and I believe that our Association, in addition to the work it does at home, should play its part on the larger stage, whatever the outcome.

For the last year, I have been honoured in being the President of a strong, healthy and united Association. I have held the office with great pride and whatever my short-comings, they would have been greater and much more noticeable but for the loyal support of Executive and Council and the ever available help and advice of our General Secretary, Dr. Routley, and his assistant, Dr. Kelly.

SPECIAL CORRESPONDENCE

The London Letter

(From our own correspondent)

Anterior Poliomyelitis

A certain amount of apprehension is being felt concerning the increasing number of cases of poliomyelitis and polioencephalitis that are being notified. Although there are no grounds for alarm, a memorandum has been issued by medical Officers of the Ministry of Health reviewing the situation and drawing attention to the action which should be taken by practitioners in dealing with suspected and proved cases. The latest figures available are those for the week ending July 26, when some 300 cases were reported in England and Wales. This is more than three times the highest figure previously recorded since the disease became notifiable in 1912—82 in one week in August 1938.

The two striking features of the disease this year are the relatively large number of cases exhibiting predominantly cerebral involvement, and the multiplicity of foci with occasional evidence of concentric spread. Although the cases are widely scattered throughout the country, with a predominance in the larger cities, particularly London, there is as yet no evidence of a country-wide epidemic.

The most disturbing feature is the early start of the "epidemic". In view of the relatively large number of cases which have occurred in July there is every reason to expect, in the words of the Ministry of Health memorandum, "an unprecedented prevalence" before the incidence of the disease normally begins to decline next month.

International Congresses

July has been a gala month for congresses. The series opened in Dublin with the International Congress of Obstetricians and Gynæcologists. As this coincided with the postponed celebrations of the bicentenary of the Rotunda Hospital, the occasion was a great event in the Irish Capital and hospitality was dispensed in a traditionally lavish Irish style. At the same time the Commonwealth and Empire Health and Tuberculosis Conference was being held in London. This was followed by the eleventh International Congress of Pure and Applied Chemistry, and once again the occasion was of double importance as it coincided with the centenary celebrations of the Chemical Society which had been postponed from 1941. What *The Times* described as "a significant omission" among the 400 papers read before the Congress was the absence of any direct reference to nuclear energy. Russia was among the 28 countries which sent delegates to the Congress.

No sooner had this Congress finished than the seventeenth International Physiological Congress opened at Oxford under the chairmanship of Sir Henry Dale. More than 1,000 delegates from over 30 countries attended this Congress, and an interesting feature of the occasion was the presentation to every member of a copy of Sir Charles Sherrington's classical work, "The Integrative Action of the Nervous System".

Venereal Disease and Conscription

In the recent debate in the House of Lords on the National Service Bill considerable attention was attracted by a speech by Lord Moran, in which he gave some alarming figures concerning the incidence of venereal disease in the armies of occupation in Germany and Japan. These figures were challenged at the time by the representative of the War Office, but the Secretary of State for War has now confirmed the correctness of Lord Moran's figures. In 1938 the annual rate of venereal disease per 1,000 troops in the British Army in Britain was 11.7. In 1946 the comparable figure was 32.8, whilst in B.A.O.R. it was 158.6. The latest figures available for this year, covering the first quarter of the year, show little change: 5.3 per 1,000 in Britain and

30 per 1,000 in B.A.O.R. Official attempts of the War Minister to minimize the significance of these figures have been coldly received, and there is general agreement with Lord Moran that it is "not fair to send immature boys abroad to do the police work of an army of occupation in a demoralized country".

ANTI-VIVISECTION

The anti-vivisectionists, like the poor, will probably always be with us, but a recent decision of the House of Lords should prove a useful check on their activities. This was a decision that a well-known anti-vivisection society is not a body of persons "established for charitable purposes only" and therefore is not entitled to exemption from income tax on investment income. Lord Wright, in delivering the principal judgment, pointed out that the only claim of the society to be regarded as charitable must be the establishment of the fact that it was beneficial to the community. What it seemed to do, however, was to destroy a source of enormous blessing to mankind.

The annual Stephen Paget Memorial Lecture to the Research Defence Society provides a useful forum for leading scientists to counteract the insidious propaganda of the anti-vivisectionists. This year Professor G. H. Woolridge was the lecturer and chose for his subject the benefits brought to animals as a result of animal research. The choice was a particularly happy one as Professor Woolridge himself was the subject of bitter attacks by the anti-vivisectionists in the days when he was investigating the problem of the induction of anæsthesia in domestic animals.

WILLIAM A. R. THOMSON

London, August, 1947.

ABSTRACTS FROM CURRENT LITERATURE

Medicine

Prevention of Postoperative Pulmonary Embolism. Evans, J. A. and Boller, J. A.: *New England J. Med.*, **236:** 392, 1947.

A series of 52 fatal cases of pulmonary embolism is reviewed and in 85% the records showed evidence that might have led to a suspicion of the condition and the institution of adequate therapy. All postoperative patients should be carefully followed to detect early evidence of thrombosis. Tenderness in the calves, an elevated temperature or pulse rate should make a thrombotic process suspect and anticoagulant therapy should be started immediately. A single injection of heparin in Pitkin's menstruum will start to be effective in two hours and will protect the patient for the two-day latent period after dicumarol administration.

Fatal postoperative pulmonary embolism is most common in the sixth decade. In this series 54% of deaths followed extensive surgery in the lower abdomen or pelvis and it is probable that anticoagulant therapy should be routine in such cases. While 52% of fatal embolism occurred between the sixth and sixteenth postoperative day it can occur before or after this period and must be continuously watched for.

Prophylactic foot exercises in all postoperative patients have been showed to lower the incidence of embolism to one-third. All such patients should wiggle their feet one thousand times a day.

Anticoagulant therapy and venous ligation are not competitive forms of treatment but should be considered complementary. Venous ligation is preferable where adequate laboratory facilities are not available for accurate estimation of anticoagulant activity. The authors limit femoral ligation to patients with thrombosis awaiting a second-stage operation; to those with any hæmorhagic tendency; to those with poor liver function; and to those with ambulatory recurrence of phlebothrombosis with pulmonary embolism.

NORMAN S. SKINNER

Rheumatic Brain Disease, Late Sequel of Rheumatic Fever. Bruetsch, W. L.: *J. Am. M. Ass.*, **134:** 450, 1947.

In recent years, attention has been directed to the occurrence of rheumatic obliterative arteritis in the brain of persons with rheumatic heart disease. This late cerebral sequel of rheumatic fever involves, mainly, the small meningeal and cortical vessels, producing gross and microscopic softening in the cortex; less frequently larger vessels are affected. The involvement of the brain may occur from several months to many years after the acute stage of rheumatic fever at a time when the person is, otherwise, enjoying good physical health. To this hitherto unrecognized cerebral process the term "rheumatic brain disease" was given.

A case of rather severe rheumatic brain disease is described, a patient of 49, with rheumatic involvement of the brain in the form of a diffuse obliterating process of the cerebral vessels — similar vascular changes were observed in the kidney.

General rheumatic endarteritis has a predilection for the smaller vessels and, in the brain, involves frequently only the small meningeal and cortical branches, resulting in microscopic areas of softening in the gray matter. The ensuing mental disturbance is determined by the personality and by the age at which the cerebral involvement occurs. If the rheumatic infection causes cerebral damage in childhood, aberrations ranging from mild behaviour disorders to slight mental deficiency states may result. In the young adult, psycho-pathologic pictures suggesting dementia præcox have been observed. The studies on rheumatic brain disease have unearthed the fact that, at autopsy, 9% of patients with dementia præcox showed signs of rheumatic infection involving the brain as well as the cardiac valves.

J. PRESTON ROBB

Report from the Cardiac Clinic of the Boston Lying-in Hospital for the First Twenty-five Years. Hamilton, B. E.: *Am. Heart J.*, **33:** 663, 1947.

During the 25 years of this report 1,335 pregnancies occurred in women with heart disease which represents 1.8% of the women treated by this hospital through pregnancy. Of these cardiac patients 93% had chronic rheumatic heart disease, 5.2% had congenital cardiovascular defects and 1.8% had miscellaneous cardiac diseases. Those with rheumatic heart disease were divided into favourable and unfavourable cases, a favourable case being one with minimal signs of rheumatic heart disease and able to carry on moderate activity without heart failure and one with no complicating diseases in themselves dangerous, such as essential hypertension, chronic bronchitis, diabetes. On the basis of his statistics the author concludes that "a pregnancy—has cost the favourable cases little, if any, more risk than their risk of death in one year of living, but it has cost the unfavourable cases a risk nearly three times greater, and those that have auricular fibrillation, a risk that is four times greater."

Among the favourable cardiac patients maternal mortality was due to bacterial endocarditis in 35% and to congestive heart failure in 12%. Among the unfavourable cases 7% died of bacterial endocarditis and 64% of congestive heart failure. Thus if patients in the latter group avoided pregnancy maternal deaths from congestive heart failure would be rare. Patients with patent ductus arteriosus and coarctation of the aorta have done well. Patients with essential hypertension have not been carefully analyzed but it is the impression that those with mild hypertension do as well as the favourable cardiac group and those

with severe hypertension do somewhat better than the unfavourable group. The stress upon the circulation is small until the sixth month when it rises to 50% above the normal. In the ninth month the stress is greatly lessened. Thus the policy of this clinic has been not to interrupt for cardiac reasons after the load of the circulation has become great, in view of the fact that the stress on the circulation will become less in the last month. A. L. JOHNSON

The Use of Anticoagulants in the Management of Acute Myocardial Infarction: a Preliminary Report. Parker, R. L. and Barker, N. W.: *Proc. Staff Meet. Mayo Clinic.* **22:** 185, 1947.

The complications which accompany acute coronary thrombosis with myocardial infarction are often the immediate effects of additional arterial thrombosis, formation of mural thrombi and embolic phenomena. In the report of Nay and Barnes (*Am. Heart J.*, **30:** 65, 1945) of 100 cases of acute myocardial infarction, thrombo-embolic complications occurred in 37%. In view of these findings and using this series as a control group, 50 consecutive cases of acute myocardial infarction were given dicumarol (alone in 50 cases), and dicumarol and heparin (10 cases). An effort was made to keep the prothrombin time between those limits which correspond to the prothrombin time of 10 and 30% prothrombin. Twenty patients had adequate anticoagulant effect within 48 hours of the onset of the infarction. In 18 a period of 2 to 5 days elapsed before a satisfactory effect was obtained, and in 12 cases there was a lapse of 5 days. Mild complications of the anticoagulant therapy occurred in 3 cases: a spontaneous hæmorrhage into the knee joint, a mild spontaneous epistaxis, and a microscopic hæmaturia. Among the 50 of the series only two patients under the effect of the anticoagulant agents had secondary vascular complications in comparison with 37% of patients who experienced such complications in the series without anticoagulant therapy reported by Nay and Barnes. A. L. JOHNSON

Some Pharmacological and Clinical Experiences with Dimethylaminoethyl Benzhydryl Ether Hydrochloride (Benadryl). McGavack, T. H., Elias, H. and Boyd, L. J.: *Am. J. M. Sc.*, **213:** 418, 1947.

The authors report their observations on more than 60 normal persons and 242 patients. Under the heading of Pharmacological Data are enumerated: (1) Antihistamine effects: the unpleasant reaction resulting from the use of histamine in gastric analyses was repeatedly relieved by the intravenous administration of benadryl; the gastric acidity was suppressed, except in 1 case, by a daily dose varying from 150 mgm. for 1 week up 400 mgm. daily for 2 weeks; as determined by fluorescin the permeability of capillaries was decreased by doses of 300 to 400 mgm. daily. It is concluded that benadryl probably "tightens" the capillaries through a neutralizing effect on the tissue-histamin. (2) Atropin-like activity: the disturbance in visual accommodation produced by benadryl following topical application simulates that of the alkaloids of the belladonna group. (3) Less well understood pharmacologic effect is its action on the cardiovascular system. In addition to decreasing capillary permeability this includes slight lowering of the blood pressure and occasional orthostatic hypotension, probably due to prearteriolar or small blood vessel dilatation; and increase in glucose tolerance.

The therapeutic results of the antihistamine action of the drug are divided into 4 groups: (1) Skin disease in which histamine is believed to play a pathogenic rôle. Of these all cases of angioneurotic œdema were completely relieved or improved, while allergic eczema and neurodermatitis responded in moderate proportion. (2) Other disease of known allergic etiology showed very good response, although less striking than in angioneurotic œdema. (3) Diseases in which an allergic element may be present showed most successful results in cases of functional dysmenorrhœa. (4) Miscellaneous conditions. In this group about half of the cases of intractable insomnia were relieved or improved, while cases of "cardiac asthma" showed a slightly lower proportion of relief or improvement. Untoward reactions observed are listed in order of frequency as drowsiness, dryness of the mouth, dizziness, weakness and fatigability, inco-ordination and lightheadedness, blurring of vision. About 50% of the patients showed one or more of these symptoms, the highest percentage occurring in those taking 150 mgm. daily. Tolerance for the drug increases rapidly during the administration. The matter of dosage is a highly individualistic one, but the necessary daily dose appears to vary between extremes of 50 to 600 mgm. in the conditions in which it was most successful, while large doses were necessary in bronchial asthma, neurodermatitis and functional dysmenorrhœa.

D. E. H. CLEVELAND

Surgery

Some Recent Advances in Pancreatic and Biliary Tract Surgery. d'Offay, T. M. J.: *Brit. J. Surg.*, **34:** 116, 1946.

Ampulla-papillary carcinoma is the group name of carcinomas of the distal inch of the common bile-duct, pancreatic duct, duodenal papilla and ampulla of Vater, since so often the site of origin is impossible to determine at operation or even under the microscope, and the treatment is the same. This carcinoma occurs in 1.13% of all carcinomas and 0.09% of all autopsies. Carcinoma of the head of the pancreas is twice as common. Ampulla-papillary carcinomas remain localized for a long time, rarely invading the head of the pancreas and are late in metastasizing to the regional lymph nodes: 24.6% of all reported cases. Carcinomas of the head of the pancreas are usually of high grade malignancy, infiltrating rapidly and metastasizing early.

Courvoisier's law has been repeatedly confirmed, but is of greater importance at peritoneoscopy or laparotomy than at the bedside since the distended gall bladder is only palpable in half the cases clinically. Absence of bile in duodenal contents and fæces and of urobilinogen in the urine signifies complete obstruction of the bile ducts. The response of the plasma prothrombin to intravenous vitamin K is valuable in the differential diagnosis of jaundice and the estimation of hepatic insufficiency. At operation, the diagnosis of the ampulla-papillary carcinomas is not difficult, but the diagnosis of carcinoma of the pancreas from chronic pancreatitis is often very difficult.

Radical removal of the growth has been done frequently only since 1937, though local removals of the ampulla-papillary growths have been done since 1898. The discovery of vitamin K, the improved prevention and treatment of shock and the work of Whipple and Cattell have resulted in the development of a safer pancreatico-duodenectomy, so that at least 125 cases have been reported since 1935.

The technique of the operation is discussed and five cases reported: one transduodenal resection of an ampulla-papillary adenocarcinoma, three pancreatico-duodenectomies for adenocarcinoma of the head of the pancreas, and one choledocho-jejunostomy for chronic pancreatitis simulating carcinoma.

Granulomas Caused by Surgical Silk and Cotton Sutures. Orr, T. G.: *Arch. Surg.*, **54:** 37, 1947.

With careful technique infection is uncommon in clean wounds following the use of surgical silk or cotton sutures. When it does occur it is usually a small stitch abscess or sinus tract. More rarely an abscess forms about suture material and this is accompanied by granulation tissue and a surrounding wall of fibrous tissue. Five cases are reported in which granulomatous lesions developed following the use of surgical silk and cotton. In the first, a 19 year old youth had an uneventful con-

valescence following repair of an indirect inguinal hernia. Four months later an abscess cavity was opened in the operative site in which several small sutures were found and hæmolytic staphylococcus was grown. The second case occurred in a 28 year old woman following a pelvic operation, and the third in a 60 year old woman following a colectomy. Abscesses developed in 21 and 10 months respectively after operation. The fourth case was one of a 67 year old man who had undergone repair of an indirect, a direct, and a femoral hernia, in which cotton sutures were used. Twenty-two months later an abscess was drained which grew hæmolytic streptococci. The last case developed an abscess in the anterior abdominal wall three months after appendectomy.

The presence of a firm indurated mass beneath the scar of operation in the absence of an acute inflammatory response, suggests the presence of a granulomatous reaction to suture material. RUPERT WARREN

Obstetrics and Gynæcology

Fetal Mortality in Cæsarean Section. Acken, H. S.: *Am. J. Obst. & Gyn.*, **53:** 927, 1947.

Fetal mortality in Cæsarean section is higher than that for vaginal delivery. An increase in autopsies in stillbirths and neonatal deaths is imperative in the interest of accurate diagnosis. If Cæsarean is indicated in cases of abnormal presentation operation should be performed early. Regional anæsthesia avoids one cause of fetal anoxia and should be widely used in Cæsarean section. Spinal anæsthesia produces greater relaxation, thereby aiding delivery and lessening trauma to the baby. Prematurity is the greatest single cause of fetal mortality in Cæsarean section. It occurs most often in connection with placenta prævia. The policy of delay in active treatment of placenta prævia might carry more infants closer to term, but widespread advocacy of this would endanger the present low maternal mortality. In cases of maternal hæmorrhage the mother should have early transfusion and the administration of pure oxygen to combat fetal anoxia. These procedures should be carried out even though there be no apparent need of them by the mother. ROSS MITCHELL

Scopolamine and Apomorphine in Labour. Hershenson, B. H. and Brubaker, E. R.: *Am. J. Obst. & Gyn.*, **53:** 980, 1947.

Apomorphine in subemetic doses and scopolamine have been used to produce amnesia and analgesia in labour in a series of 500 patients at the Boston Lying-in Hospital. The effectiveness of this drug combination compares very favourably with other measures. The average primiparous labour in this series was 11.3 hours. The average multiparous labour was 6.5 hours. Apomorphine-scopolamine premedication does not appear to influence the third stage of labour; blood loss compares favourably with other reports appearing in the literature. The combination exerts no demonstrable depressant effect on either full-term or late premature infants. It may be administered by any route. On the whole, this combination is better from both maternal and fetal standpoints than other methods employed at this hospital. ROSS MITCHELL

Riboflavin Deficiency in Pregnancy. Brezezinski, A., Bromberg, Y. M. and Braun, K.: *J. Obst. & Gyn. Brit. Emp.*, **54:** 182, 1947.

It has been demonstrated in animals that lack of riboflavin in the food may lead to relative sterility and when reproduction was possible, to resorption of the product of conception (Warkany and Schraffenberger, 1944). Evidence is also available that riboflavin deficiency may cause congenital anomalies of the offspring (Warkany and Schraffenberger, 1943; Johnson *et al.*, 1945). A significant relationship was found to exist between riboflavin deficiency and the incidence of prematurity. The average incidence of premature deliveries in the groups with low riboflavin excretion was 14.6% while in the two remaining groups it was only 5.5%. Very significant results were also obtained regarding the incidence of stillbirth due to antenatal death of the fetus. In the first two groups antenatal death occurred in 4.9% of the cases, while in the other groups there was none at all. It appears also that riboflavin deficiency has a harmful effect on lactation. In group A 33.3% of the cases had hypogalactia and in 6.6% there was complete agalactia. In group B 25.5% had hypogalactia while in group C and group D an average of only 5.9% was noted. P. J. KEARNS

Some Factors Causing Difficult Labour in Multigravidæ. Williams, B.: *J. Obst. & Gyn. Brit. Emp.*, **54:** 187, 1947.

A series of 23 patients is reviewed in whom difficult or obstructed labour occurred in their 8th or subsequent pregnancy after a previously normal obstetrical history. The main factors responsible for the difficulty were found to be a small pelvis and a large baby. Evidence is brought forward that the pelvic contraction is due to a mild form of osteomalacia. P. J. KEARNS

The Interpretation of Tests for Renal Function. Brentnall, C. P.: *J. Obst. & Gyn. Brit. Emp.*, **54:** 172, 1947.

The post-toxæmic state is a real condition and not merely something that exists in a laboratory report. The duration of this state is generally longer than is generally thought. So far as the cases that have been shown are concerned it seldom lasts less than 7 months and is usually detectable up to one year. The factors which decide whether the patient makes a good recovery from this condition or passes on to the secondary hypertensive state are probably multitudinous. Possibly the two most important are: (1) The amount of rest that the patient can get during the first few months after delivery. War and post-war conditions obviously do not help the unfortunate mothers in this respect. This imponderable aspect will not, therefore, be discussed further. (2) The duration of raised blood-pressure due to the pregnancy toxæmia. Secondary hypertensive changes following the post-toxæmic state seem to occur far more frequently in those cases where the blood-pressure has remained high and pregnancy allowed to continued in the hope of getting at least one live baby for the anxious mother. The length of time during which the blood-pressure remains high seems to be a far more important factor than the very great heights to which it may rise. The late toxæmic with a very high blood-pressure, culminating possibly in eclampsia may have a prolonged post-toxæmic state, but rarely develops secondary hypertensive changes.

P. J. KEARNS

Cancer of the Cervix Uteri—Results of Treatment with Radium. Maliphant, R. G.: *J. Obst. & Gyn. Brit. Emp.*, **54:** 155, 1947.

The results of radium treatment in a series of 827 cases of cancer of the uterine cervix are presented. (1) Interstitial radium treatment showed a 5-year salvage figure of 11%—it was satisfactory only in cases in which the disease was limited to the cervix. With the two-application Stockholm technique, the absolute 5-year survival rate was 25.2%; (2) 15% of the women surviving 5 years died of cancer during the succeeding 5-year period, and even 10-year survival after radiotherapy is not synonymous with cure; (3) the best results were obtained in the hypertrophic growths. They produce symptoms earlier than do growths of the infiltrating type, but they have a more favourable prognosis irrespective of the clinical stage of the disease; (4) the prognosis in adenocarcinoma of the cervix is not so favourable as that in squamous-cell cancers, in spite of their tendency to develop as hypertrophic or cauliflower growths. The best results were obtained in the more anaplastic squamous-cell cancers the mid-ripe transitional-cell types and the unripe spindle-cell types; (5) the duration of symptoms was a poor index to the extent of the disease

and therefore to the prognosis; (6) the presence of pain does not invariably indicate advanced disease, but at all stages it has an adverse influence on the prognosis. P. J. KEARNS

Dermatology

The Place of Health Resort Therapy in Dermatologic Disorders. Cipollaro, A. C.: *J. Am. M. Ass.*, **134:** 249, 1947.

Ordinary cutaneous diseases are usually well managed at home by the experienced dermatologist but certain cases belonging to chronic, recurrent, recalcitrant and generalized categories can profit by the additional resources furnished by resort therapy. It is essential that a resort undertaking to handle these cases should have a fully qualified dermatologist in residence, having complete equipment for various types of physical therapy, including x-ray and facilities for biopsies, bacteriologic and mycologic studies. The advantages additionally offered by a health resort are the change of general and immediate environment, a scientifically regulated regimen and therapeutic waters. The author enumerates a group of cutaneous diseases which should respond better under ideal resort conditions as follows: acne cachecticorum (conglobata); idiopathic exfoliative dermatitis; dermatitis medicamentosa due to drugs taken for constipation and insomnia, which benefit by removing the necessity for resort to such drugs; generalized neurodermatitis, and generalized or recalcitrant localized seborrhœic dermatitis; chronic recurrent multiple furunculosis; postzoster neuralgia; chronic recurrent lichen planus; cutaneous neuroses; idiopathic pruritus; severe psoriasis; cutaneous tuberculosis; chronic slow-healing non-specific ulcers; chronic urticaria and certain vascular diseases such as Raynaud's syndrome, pernio- and sclero-derma. The author emphasizes that a hotel at the seaside or in the mountains with hydrotherapy apparatus and a solarium does not constitute a health resort and is useless for treatment of cutaneous diseases. A warning note against the dangers of drinking or bathing in radioactive waters is also added. D. E. H. CLEVELAND

Actinomycosis of the Face and Neck. Lamb, J. H., Lain, E. S. and Jones, P. E.: *J. Am. M. Ass.*, **134:** 351, 1947.

Cutaneous actinomycosis is most frequently seen about the mouth. Sixteen cases of cervicofacial actinomycosis of which 15 were secondary in type are discussed. The primary form is comparatively rare. In the discussion of the causative organism a simple classification of the actinomycetes is given and Guy's opinion that actinomycosis of the skin is a definite clinical entity in which the ray fungus is always present and is distinguishable from that presented in the tissues by the non-spore-bearing anaerobe, is accepted. In considering etiological factors the authors state that the straw-chewing theory, while not to be ignored, has been overstressed. *Actinomycosis bovis,* accepted by most investigators as the etiological agent in head and neck infections has not been found capable of producing spores or otherwise maintaining growth in organic matter. It is emphasized that not all species of pathogenic actinomycetes produce club-bearing granules, and other infections, such as *Coccidiodes immitis* and strains of *Aspergillus, Sporotrichum* and *Monilia* under certain conditions produce granules; thus granules must be crushed and stained for examination before pronouncing the disease to be actinomycosis. Three types of granules, including the sulphur granules appear in a definite chronologic order and their crushed appearance is described in detail, together with photomicrographs. The onset of the disease is usually insidious, and usually a history of chronic peridontitis about carious teeth goes back for several years. Exacerbations and regressions of swelling and pain alternate during which the fungus probably migrates to bone and soft tissues along with secondary bacterial contamination. The patient becomes hypersensitive to the actinomycetes, the resulting actinomycosis being an allergic reaction to a common parasitic inhabitant of the mouth, teeth and tonsils. The acute stage usually supervenes upon the removal of infected or pulpless teeth. In subacute cases the firm, purplish, subcutaneous tumours appears, later softening and breaking down with fistulous tracts. In the acute form a rapid dense œdema extends from jaw to clavicle with livid erythema and central necrosis but little true pus, and multiple sinuses form with increasing secondary bacterial invasion. Differential diagonsis must exclude tuberculous and syphilitic gumma, blastomycosis and metastasis from a cutaneous epithelioma. The best treatment was found to be filtered roentgen radiation with sulfadiazine by mouth. D. E. H. CLEVELAND

An Eruptive Fever Involving the Skin and Mucous Membranes (Stevens-Johnson Disease). Patz, A.: *New England J. Med.*, **236:** 697, 1947.

The author describes a disease, with an illustrative case, which has been reported under various titles such as "erythema multiforme bullosum with involvement of the mucous membranes", "mucosal respiratory syndrome"; and "erythema multiforme pluriorificialis". Contrary to some observers who consider that the mucosal involvement is only a symptom of erythema multiforme and should not entitle it to be classed as distinct entity, the author considers that this underemphasizes the more important features, and the syndrome should be regarded as a separate disease. For it he proposes the eponymic name of Stevens-Johnson disease, after the authors who supported this view in describing 2 cases in 1922 of "a new eruptive fever associated with stomatitis and ophthalmia". The disease usually is characterized at onset by a mild conjunctivitis and stomatitis, followed in a day or two by fever, prostration and a generalized erythematous eruption which usually is vesicular or hæmorrhagic. The stomatitis soon becomes bullous and the conjunctivitis severe with a copious purulent discharge. Corneal ulceration and more serious and incapacitating ocular complications may occur. Two fatal cases have been reported. The mucosal lesions generally resolve in 2 weeks and the skin lesions in 3 weeks. Etiology is unknown. About a third of reported cases are over 15 years of age and incidence in the male preponderates by 5 to 1. There is no characteristic blood picture. Although the author's case showed a thick yellowish exudate about the urethral orifice and corona glandis, he makes no reference to the involvement of the nares, naso-pharynx, anal and vulvar orifices which commonly form part of this syndrome. D. E. H. CLEVELAND

Herpes Zoster Appearing After Trauma. Klauder, J. V.: *J. Am. M. Ass.*, **134:** 245, 1947.

Herpes zoster appearing after peripheral nerve injury, often trivial, is of importance in view of laws governing workmen's compensation. The author reviews a number of cases from the literature affecting the surface of the skin or cornea in order to illustrate certain features. With few exceptions the herpes zoster affected the nerve supplying the area injured. In 2 cases the eruption appeared within 24 hours after the injury and in 2 others it appeared about one month after the injury. In others the incubation period varied from 36 hours to 7 days. Eight cases of herpes zoster ophthalmicus have been collected from the literature and reviewed by Ammann in 1935, and in the 5 of these cases in which the interval between the injury and appearance of the herpes zoster was given the period varied from 3 to 8 days. Generalized herpes zoster has also been observed after injury, and localized herpes zoster has also been reported following various types of deep injury to a nerve or a ganglion, such as intramuscular injections, deep radiotherapy, pressure of pathologic processes and osteopathic manipulation of the spine. The author reports 8 cases observed by him. In these the disease occurred after an interval from the injury varying from 1 to 9 days. In some cases sensory disturbance appeared during this interval. The questions whether

Ayerst

FOR THEIR PROTECTION

Vitamins essential for proper growth and development are readily available in Ayerst biologically-tested Vitamin A and D products.

"ALPHAMETTES"
"ALPHAMETTE" LIQUID
AYERST COD LIVER OILS

Ayerst

AYERST, McKENNA & HARRISON LIMITED • *Biological and Pharmaceutical Chemists* • MONTREAL, CANADA
445

the injury acts by producing a *locus minoris resistentiæ* for the action of a virus already existing in the body; the introduction of a virus at the time of injury with resultant ascending infection of a nerve; or an involvement of the nerve by a hæmatogenous transfer of the neurotropic virus, are discussed. Experimental evidence and clinical observations indicate that the incubation period of herpes zoster varies from a few days to about 2 weeks. In the cases reported or reviewed from the literature the interval has varied from 1 day to 3 weeks. It is considered reasonable to conclude that trauma may precipitate herpes zoster and that the longer the interval between the trauma and the eruption is prolonged beyond 3 weeks the greater is the probability of the noncausal rôle of trauma. D. E. H. CLEVELAND

Allergic Manifestations After the Injection Treatment of Varicose Veins. Melkon, E. A. and Scheidell, D. K.: *New England J. Med.*, **236:** 941, 1947.

Six patients had veins injected. In 3 quinine and urethane, in 2 sodium morrhuate and in 1 sylnasol were the sclerosing solutions used. In each of these patients the first injections evoked no allergic reaction, but with one exception a later injection of the same material after an interval varying from a few months to a few years resulted in complaints of sudden warmth and weakness and a precipitate fall of blood pressure to a systolic level of 40 to 80, while in all but one of these no diastolic could be recorded. Coincidently a generalized urticarial eruption appeared. In the one exception referred to the reaction followed after the 4th weekly injection of quinine urethane. Three patients who had reacted allergically to quinine and urethane later received other injections, in 2 cases sylnasol and in the other sodium morrhuate. In each case similar allergic reactions occurred after 3 or more injections of the sclerosing solution, although in the case of the sylnasol scratch and intradermal tests of the solution had been negative. D. E. H. CLEVELAND

Industrial Medicine

Early Treatment of Ocular Injuries. Derrick, V.: *Indust. Med.*, **16:** 173, 1947.

The importance of early and adequate treatment of ocular injuries is stressed in this article, which is the report of a talk presented in Chicago at the October, 1946, meeting of the American Association of Railway Surgeons. The author explains briefly the harm apt to result from various injuries and gives certain specific rules which he considers of value to those handling them. A lid laceration should be approximated accurately and with skill. It is necessary to clean the wound, then approximate its edges; sutures should be placed in such a position that there is a small inverted V which will in time smooth down. Any injury of the conjunctiva should be left to the eye surgeon. Burns of a chemical nature should be treated by copious irrigation of tap water or saline. In the opinion of the author, the use of a chemical to neutralize acid burns is a fallacy because by the time it can be put in the eye it is too late. A small corneal laceration should be irrigated with saline and an antiseptic solution such as sulfathiazole 5% instilled. If there has been penetration of the cornea by a foreign body, prompt treatment and adequate after-treatment is very important. After the eye has been thoroughly cocainized, the foreign body should be removed with a good loupe and any rust left behind, by the use of a dental bur. Following this, 5% sulfathiazole ointment or penicillin ointment is all that is necessary. The eye should be covered with a bandage and the patient told to return the next day.

Penetrating injuries of the eye are very serious; they require the expert care of a trained ophthalmic surgeon. Removal of the foreign body depends on determination of its size and shape and of its exact location. If magnetic, it may be removed with a magnet; otherwise with forceps. Contusion of the eye following an explosion or after being struck with a blunt object involves serious possibilities. The eye should be bandaged and the patient sent to the ophthalmic surgeon.

MARGARET H. WILTON

The Division of Industrial Hygiene. Tourangeau, F. J.: *Bulletin Sanitaire*, **47:** 21, 1947.

The dangers to the health of workers, caused by both chemical and physical agencies, constitute a serious problem. The medical and hygienic aspects must be considered not only in the light of the frequency of strictly occupational diseases, but also in the light of the aggravation of an illness already existing and of a gradual and insidious deterioration of the workers' health. In this article the author who is director of the Division of Industrial Hygiene in the Province of Quebec, discusses the rôle of that organization in furthering industrial hygiene in that province. He relates briefly its establishment in 1936 and the development during the next few years. A survey of more than 3,300 establishments was conducted in order to secure a representative picture of working conditions and of existing dangers to health. This served as a basis for the establishment of an efficient program of prevention of industrial diseases.

After outlining the operation and activities of the Division and its personnel, he reviews the problems as found in Quebec during recent years. More important among the large number of major conditions of potential health dangers are the following: noise, humidity, dry or radiant heat, dust, particularly silica and asbestos, occupational dermatitis, and toxic substances liable to bring on chronic poisoning. The most serious in this latter group are lead, benzol and mercury. The effects produced by each of these conditions are presented briefly, together with the medical and technical remedial measures suggested. In view of the hazards involved, the Provincial Ministry of Health have made regulations in connection with the use of certain toxic products. The necessity of employers taking preventive measures is stressed. Compulsory periodical medical examination for all employees who work under dangerous or potentially unsafe conditions and periodical voluntary examination of all others, constitute the first preventive measure to be adopted. It is also recommended that every plant physician who suspects the existence of a dangerous working condition should avail himself of the technical medical service which the Provincial Ministry of Health places at the disposal of industry for the purpose of ascertaining the extent and the nature of the danger, as well as the means to be employed for its elimination.

MARGARET H. WILTON

OBITUARIES

Dr. A. B. Cooke died on June 17 at Lloydminster. He was born September 4, 1888, graduated from Queen's University in 1912, and began his practice in Michigan and New York State in 1914. He saw service overseas in the first Great War, and later joined his brother in practice at Lloydminster. At the outbreak of the Second World War he offered his services and was for a time stationed at points in Western Canada. Resuming his practice at Lloydminster about three years ago, he sustained a severe coronary episode from which he made a satisfactory recovery and resumed his work until a second heart attack culminated in his death.

Dr. Cooke was an ideal type of general practitioner, capable, conscientious and unsparing of himself in the services that he gave to the people of Lloydminster and the large area tributary to that centre. He will be greatly missed by the many patients and friends in the community in which for so many years he lived and laboured.

Dr. P. C. Crosby died in Montreal on June 29. He came to Melville in 1904 and practised as a physician

Introducing

'PENEUCIN'

TRADE MARK BRAND

PENICILLIN OINTMENT

We take pleasure in announcing the introduction of 'PENEUCIN' brand penicillin ointment, in which penicillin is compounded with 'Eucerin' Anhydrous, our well-known brand of Ung. Alcoh. Lanae.

'PENEUCIN' is a stable, elegant and non-irritant ointment that can confidently be prescribed whenever penicillin ointment is required.

'PENEUCIN' is indicated for the treatment of staphylococcal and streptococcal infections of the skin, e.g. Sycosis barbae, impetigo, secondary infected eczema.

'PENEUCIN' is supplied in tubes of 30 grammes, each gramme containing 1000 units of penicillin (calcium salt).

(M.30)

HERTS PHARMACEUTICALS LTD., WELWYN GARDEN CITY, HERTS, ENGLAND

Distributing Agents: Messrs. VANZANT & COMPANY, 357 COLLEGE ST., TORONTO, ONTARIO

and surgeon there until his retirement, due to ill health in 1944. He left Melville in 1945, residing for a short time in Winnipeg, and later moved to Montreal, where he resided, until his death, with his son, Dr. Clayton Crosby.

He was born at Marshfield, Prince Edward Island in 1876. Widely known here, where for so many years he was active in all community endeavours, his death will be widely mourned by hundreds of friends and acquaintances, not only in Melville and district, but throughout the West.

Dr. William J. Defries died on July 20 at his home in Toronto.

For some time engaged in general practice, Dr. Defries was appointed in charge of the anæsthesia services of the former Grace and Toronto Orthopædic Hospitals. Later he was compelled, because of ill health, to retire from active practice.

Dr. Defries was also recognized as an authority in the field of medical insurance. He was medical director of the Mutual Benefit Health and Accident Association. He was one of the charter members of the Canadian Society of Anæsthetists, in which he had held office for many years. He was a Fellow of the Academy of Medicine, Toronto, and a member of the Granite Club.

Surviving are his widow, a son and a brother.

Dr. Nelles Thomas George of Rosetown, Saskatchewan died on July 19 at his home, at the age of 59. Dr. George was born at Iona, in Elgin County, Ont., and graduated in medicine from Western University in 1911, after spending two years teaching in the west. He practised in Saskatchewan since 1912, in and around Rosetown district. He leaves a widow, two sisters and two brothers. All through his career he was interested in sports, including hockey and baseball. At Outlook in 1920 he was the manager of the local hockey club. He was a member of Rosetown Masonic Lodge, and also a member of the Elks lodge, Rosetown.

Dr. E. J. Gordon, aged 57, of St. George, died on July 13 in Brantford General Hospital. He graduated in medicine from Queen's University in 1920.

Dr. Frederick William Hart, pioneer western physician, whose practice at Indian Head extended over a period of 40 years, passed away at Vancouver on May 21, 1947. The funeral service was at Vancouver with burial in the Masonic cemetery there. The late Dr. Hart retired to the Coast about a year ago.

Dr. Hart had come to Indian Head in 1905, just three years after the town was incorporated. One of the earliest doctors in that district, he was known well throughout the province. Surviving, besides the widow, are three sons, two daughters, five sisters and a brother.

Dr. Hart was born in Pugwash, Nova Scotia, in 1877 and received his early education in the public schools and later in Mt. Allison Academy, eventually attending university at Sackville, N.B. He secured his B.A. degree in 1898 and then attended McGill University, graduating in medicine in 1902. For a year he carried on a practice in New Brunswick and then went to Saint John, N.B., as assistant to a Dr. Price. In 1905 the spirit of the West captivated the young physician and he came to the prairies. After looking over the territory from Winnipeg to the Rockies, he decided his best service could be given at Indian Head, for which community he achieved an abiding affection as the years passed. In 1915 he volunteered for overseas service and served for a year with the R.A.M.C. in Cairo, Egypt. He resumed his practice at Indian Head in 1916 and in 1922 obtained his degree of F.A.C.S. Dr. Hart had always maintained the keenest of interest in municipal affairs and in Board of Trade work. For several years he served on the Collegiate board and for six years on the town council, during two of which (1923-24) he was mayor. For a number of years he was also medical health officer for both the town of Indian Head and the rural municipality. He had served as president of the Indian Head Board of Trade and represented Saskatchewan on the Canadian Medical Board. He was a Past Master of the Indian Head Lodge, A.F. & A.M., and a member of the Scottish Rite, Regina.

Dr. Harry Miles Kinsman died at his home in Hamilton on June 6. He is survived by his widow.

Dr. J. S. McCallum died suddenly at Shawnigan Lake on July 13.

He served for many years with the Soldiers' Civil Re-Establishment Commission, and had been assistant district administrator and assistant chief medical officer for the Canadian Government since 1935. Dr. McCallum had been in charge of the medical service of the Department of Veterans' Affairs at the Belmont Building since 1945. He was at one time medical health officer for the municipality of Esquimalt.

Dr. S. Cameron MacEwen, founder of British Columbia's non-profit Medical Services Association, died suddenly at his home in New Westminster, June 18, of coronary thrombosis.

Both as a private practitioner and in his position, in 1940, as president of the College of Physicians and Surgeons, he persistently advocated a health insurance plan to guarantee doctor's care to workers and their families for sickness and accidents. When the M.S.A. incorporated, he headed it as medical director and retained this post until his death.

Born in Thurso, Que., in 1882, he graduated from McGill in 1909, and spent most of his life in practice in New Westminster, B.C.

Surviving are two daughters, a son, a sister and two brothers.

Dr. J. Alton Ross died at his home in Salisbury, N.B., July 27, after a three months' illness. He was born in Stellarton, N.S., graduated in Medicine from Dalhousie in 1941, and practised shortly in Albert and Salisbury, N.B. He joined the R.C.A.M.C. in 1943 and served in Canada and Overseas particularly on the Medical Staff of the Hospital Ship *Lady Nelson*. Dr. Ross was highly esteemed in his practice and by his medical colleagues.

Dr. Helen Ryan, the first woman doctor to be granted membership by the Canadian Medical Association, died on July 6.

Dr. Ryan was also the first woman accepted and the first woman to graduate from medical school at Queen's University.

Born in Mt. Forest, Ont., on June 7, 1860, Helen Reynolds attended the public school there and the Ottawa Normal School before enrolling in the medical class at Queen's. She graduated in 1885, passed provincial and state medical boards and opened an office in Toronto.

Four years of struggle to become established followed, then she joined her brother in Mt. Forest and they opened a combined office there.

In 1890 she married Thomas John Ryan and went to Sudbury, Ont., to live. In the next 17 years she carried on an extensive medical practice, took care of her home and raised five children.

The Ryan family came west to Victoria in 1907 and officially from that time Dr. Ryan was on the retired list.

With her family grown up, Dr. Ryan turned her keen mind to public affairs. She took part in early efforts to achieve the women's franchise and joined the Local Council of Women and travelled extensively throughout British Columbia, addressing Women's Institutes. She was a member of the original convocation of the University of British Columbia and a charter member of the University Women's Club, being their fourth president and holding one of the four life memberships the club has given.

Dr. Charles Sheard died on July 12 at the Toronto East General Hospital, after a brief illness. Born in Toronto, he received his early education at the Model

CRYSTALLINE PENICILLIN *G*

It has been widely established that Penicillin *G* is a highly effective therapeutic agent. The crystalline form of Penicillin *G* prepared and supplied by the Connaught Medical Research Laboratories is highly purified. Because of this high degree of purity, pain on injection is seldom reported and local reactions are reduced to a minimum. Crystalline Penicillin *G* is heat-stable, and in the dried form can be safely stored at room temperature for at least three years.

PHOTOMICROGRAPH
OF PENICILLIN CRYSTALS

HOW SUPPLIED

CRYSTALLINE PENICILLIN G IN VIALS

Highly purified Crystalline Potassium Penicillin *G* is supplied by the Laboratories in sealed rubber-stoppered vials of 100,000, 200,000, 300,000 and 500,000 International Units. No refrigeration is required.

CRYSTALLINE PENICILLIN G IN OIL AND WAX (ROMANSKY FORMULA)

A heat-stable and conveniently administered form of Crystalline Sodium Penicillin *G* in peanut oil and beeswax is available in 1-cc. cartridges for use with B-D* disposable plastic syringes, or as replacements with B-D* metal cartridge syringes. Each 1-cc. cartridge contains 300,000 International Units of Crystalline Sodium Penicillin *G*.

* T.M. Reg. Becton, Dickinson & Co.

CRYSTALLINE PENICILLIN G IN TABLETS FOR ORAL USE

Buffered tablets of Crystalline Sodium Penicillin *G* are distributed by the Laboratories in tubes of 12. Two strengths are supplied, 50,000 and 100,000 International Units per tablet. No refrigeration is required.

CONNAUGHT MEDICAL RESEARCH LABORATORIES
University of Toronto Toronto 4, Canada

School and Upper Canada College. Following his graduation from the Medical School of the University of Toronto in 1910 he took postgraduate work in New York, where for two years he served on the staff of Blackwell's Island Hospital. Later he spent some time in study in England, where he received the degree of member of the Royal College of Physicians of London in 1918.

During the First Great War Dr. Sheard saw service as a captain for three years with the C.A.M.C. He was for 20 years on the faculty of the University of Toronto Medical School, resigning in 1939. As a young man he was an enthusiastic oarsman and was a member of the Argonaut Rowing Club.

Surviving are two sons and two brothers.

Dr. Alexander Smith, graduate of Queen's Faculty of Medicine in 1902, died on July 2 in East Orange, N.J. He was born in Kingston, Ont.

One sister and one brother survive.

Dr. Clifford Tisdale died at Orillia, Ont., on July 16. He graduated in medicine from Queen's University, Kingston, in 1933. He is survived by his widow.

Dr. William Austin Werden died at his residence in Mimico, Ont., June 30, in his 66th year. A graduate of the University of Toronto in 1918, Dr. Werden was a resident of Mimico for many years. After graduation he continued in postgraduate study in England and France, and received the diploma in public health at Cambridge. On his return to Canada he practised at Maynooth.

Surviving are his widow, a brother and a sister.

Dr. Charles Hunter Wilson died on June 8 at the Toronto General Hospital. He is survived by his widow.

News Items (Continued from page 292)

Manitoba

Dr. Harry Coppinger, superintendent of the Winnipeg General Hospital has made an urgent appeal for donors to the blood bank which supplies all the hospitals in the city including Deer Lodge, the D.V.A. hospital.

Dr. H. W. Lewis, medical officer for Arctic areas, who was a passenger on the Hudson's Bay Company's ship *Nascopie*, wrecked off Cape Dorset, Baffin Land, arrived in Winnipeg by plane on August 1. He predicts that in the near future medical inspection trips in the Arctic will be made by air. ROSS MITCHELL

New Brunswick

Dr. J. A. Finley has begun practice in Saint John and has assumed his appointment on the surgical service of the General Hospital.

Dr. John Palmer, of Calgary, spent the holiday season visiting friends in his native province of New Brunswick. His medical friends in this province heard from him of other friends in the Golden West.

To July 22, six cases of polio had been reported in New Brunswick, so far the type of case has been mild.

Dr. J. C. "Jock" MacKenzie has spent some weeks making a survey of the hospital situation in Moncton. Already some of his recommendations have been submitted to the Board of the Moncton City Hospital. An extensive building program for this hospital seems indicated. A. STANLEY KIRKLAND

Nova Scotia

The Annual Dalhousie University Refresher Course for physicians of the Maritime Provinces and Newfoundland will be held this year at Halifax from October 6 to 10 inclusive. As usual it will coincide in point of time with the annual meeting of the Medical Society of Nova Scotia. It is hoped that the official opening of the new Victoria General Hospital will take place shortly.

The Refresher Course is intended primarily for general practitioners of medicine, and the program this year covers this field in a satisfactory manner. Members of the Faculty of Medicine will be assisted by Dr. G. R. Brow, Professor of Clinical Medicine at McGill University; Dr. E. M. Robertson, who is Professor of Obstetrics and Gynæcology at Queen's University, and Dr. H. I. McLaughlin, Assistant Professor of Clinical Orthopædic Surgery at Columbia University.

Dr. H. C. Read, Resident in Medicine on the Staff of the Victoria General Hospital, Halifax, has been awarded one of the six Nuffield Fellowships alloted to Canada this year. He has been assigned to work with Dr. Janet Vaughan in hæmatology. A graduate of Dalhousie University Medical School in 1943, he saw active service with the R.C.A.M.C. in England and on the Continent. Accompanied by Mrs. Read he will go to England in the early autumn to begin his work.

Dr. E. F. J. Dunlop, a graduate of Edinburgh University has opened a practice in Bridgewater, giving special attention to diseases of the eye, ear, nose and throat.

Dr. G. H. Cox of New Glasgow in his rôle as a naturalist is often called upon to solve unexpected problems. The story goes that a mysterious beetle bit a dog, in a nearby town, followed almost at once by the demise of the canine. Notwithstanding, the heroic onlookers snared the bug and brought it to Dr. Cox for identification. After inspecting it from all angles, the doctor pronounced it a common water beetle, and harmless. Now—what killed the dog?

H. L. SCAMMELL

Ontario

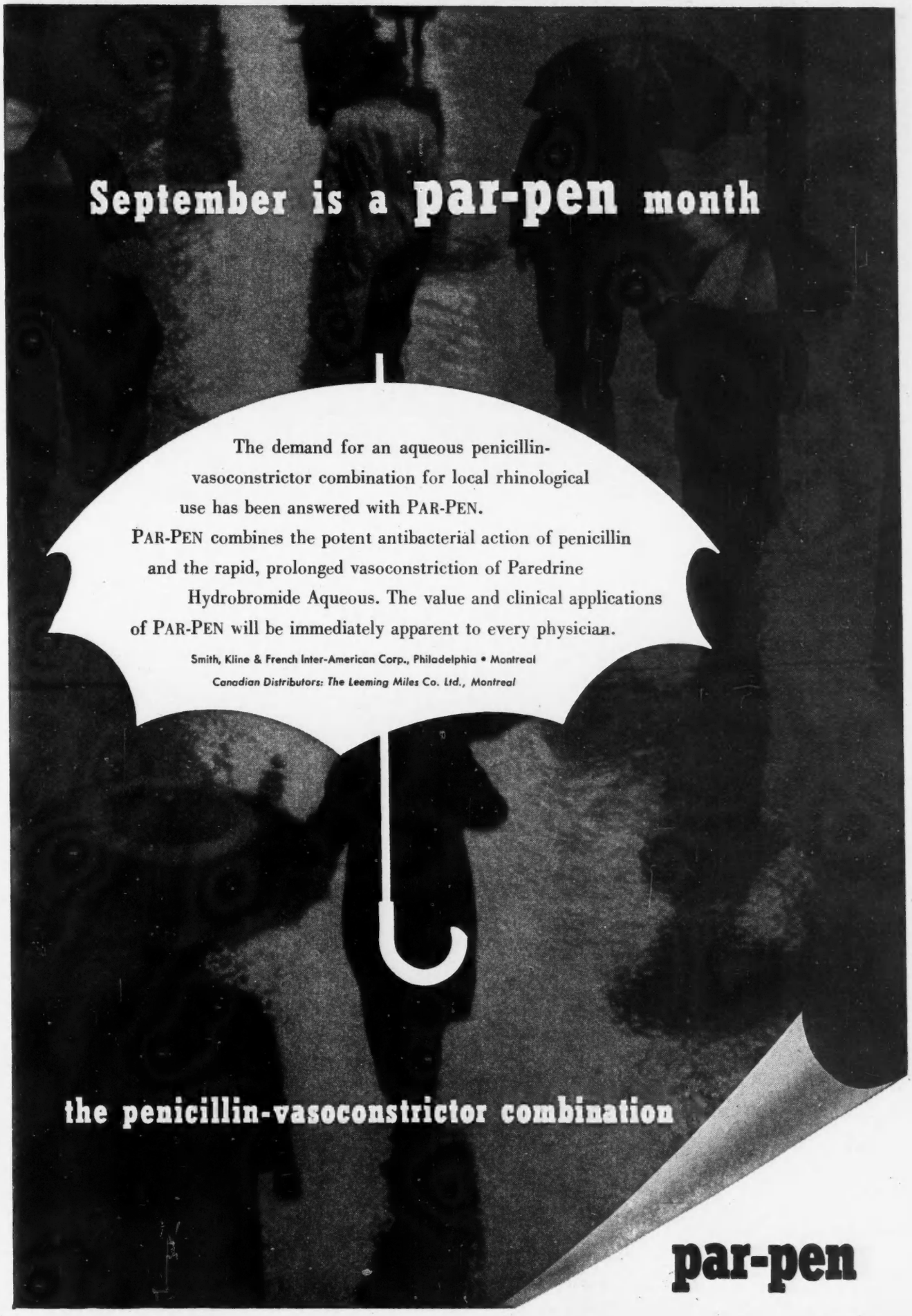
Dr. J. W. Tice of Hamilton, Ontario, was elected president of the Aero Medical Association at Atlantic City recently. He succeeds Rear Admiral J. C. Adams of the United States Navy, while Dr. Marion M. Kalez of Spokane, Wash., was named president-elect.

Dr. Kenneth E. Down of Montreal was elected to the association executive committee, together with Major General Malcolm C. Grow of the United States Army, and Dr. William B. Smith of Hartford, Conn. The association, during its meetings, criticized lack of uniformity in the United States civil aeronautics authority's medical examinations for commercial and private pilots.

Four generations of the Storms family attended a party and reunion on July 4 on the 90th birthday of Dr. Douglas G. Storms, one of Hamilton's leading physicians. The doctor practised medicine in Hamilton after his graduation from Queen's University in 1886 until his retirement in 1938.

Dr. Storms has occupied himself with his garden and his hobby of making wooden cribbage boards during the war. He sent thirty-two hundred of these boards to Canadian service camps and units at home and overseas. LILLIAN A. CHASE

Dr. James Masson formerly chief in the Division of Surgery, Mayo Clinic, Rochester, Minn., was a visitor in Toronto while on his vacation in July.


September is a par-pen month
The demand for an aqueous penicillin-vasoconstrictor combination for local rhinological use has been answered with PAR-PEN.
PAR-PEN combines the potent antibacterial action of penicillin and the rapid, prolonged vasoconstriction of Paredrine Hydrobromide Aqueous. The value and clinical applications of PAR-PEN will be immediately apparent to every physician.
Smith, Kline & French Inter-American Corp., Philadelphia • Montreal
Canadian Distributors: The Leeming Miles Co. Ltd., Montreal
the penicillin-vasoconstrictor combination
par-pen

Dr. E. Stanley Ryerson of Toronto has been awarded the King Haakon VII medal. It was presented by Mr. Odegard Omejer, Norwegian Consul to Toronto. The citation reads in part "It is hardly necessary to explain, as the high esteem you were held in by the medical officers of the Norwegian Air Force is well known and also the kind of assistance you rendered our young medical students here during the war". Dr. Ryerson, Professor of Health and Physical Education in the University of Toronto was assistant Dean of the Faculty of Medicine when he rendered the services so graciously acknowledged by the Government of Norway.

Dr. William A. Scott lately professor of Obstetrics and Gynæcology in the University of Toronto attended the bicentenary of Rotunda Hospital in Dublin and took part in the program of events celebrating the occasion.

M. H. V. CAMERON

Saskatchewan

The Saskatchewan Medical Convention is being held in Regina at the Trianon Ballroom, as the Hotel Saskatchewan is not available this year, on September 8, 9 and 10. It is the fortieth annual meeting of the College of Physicians and Surgeons. Regina and Moose Jaw District Medical Societies are to be co-hosts. The team of C.M.A. speakers will supply the scientific lectures, and Dr. F. G. McGuinness, President of the C.M.A., and Dr. A. D. Kelly, Assistant Secretary of the C.M.A. will also be present. Chairmen of Committee on Arrangements are Dr. B. C. Leech of Regina and Dr. E. R. Stewardson of Moose Jaw.

A newly organized District Medical Society has been set up at Humboldt, with Dr. J. M. Ogilvie as President and Dr. M. G. Kunkel as Secretary. The organization meeting took place on May 21, 1947, and will include the Doctors from Viscount, St. Brieux, Leroy, Watson, Spalding and Quill Lake.

The many friends of Dr. E. B. Alport of Regina, will be glad to learn that he has regained his good health and has returned to his practice.

New registrations in Saskatchewan include Dr. J. M. Goodman, Alberta, 1939, at McKague; Dr. J. C. Dundee, Manitoba, 1945, on the staff of the Saskatoon Sanatorium, Dr. A. V. Goldstein, Toronto, 1944, at Watson; Dr. J. E. Wittig, Western Ontario, 1946, at Wishart; Dr. V. D. Junek, Manitoba, 1945, at Yorkton; Dr. Max Minuck, Manitoba, 1946, at Lafleche; Dr. B. Krakauer, Toronto, 1946, at Gladmar; and Dr. F. S. Lawson, Toronto, 1928, recently appointed Superintendent of the Weyburn Mental Hospital, and replacing Dr. A. D. Campbell who has retired.

Dr. F. C. Middleton, who retired recently from the staff of the Department of Public Health, has been named President-commissioner of the St. John Ambulance Associaton, Saskatchewan branch. He has been associated with St. John Ambulance work for many years and will now be the first to hold the office of president-commissioner which has amalgamated with St. John Brigade Association.

Dr. F. H. McKenzie of the Regina Cancer Clinic and Dr. C. C. Burkell of the Saskatoon Cancer Clinic, are taking postgraduate work at the Holt Radium Institute, Manchester, England.

Dr. A. B. MacDonell and Dr. E. W. Spencer have opened an office together in Saskatoon, for the practice of radiology.

B. BRACHMAN

General

The Osler medal in historical medicine has been awarded only three times. In 1946 it was won by Peter Kellaway, and in 1947 by Miss Honor M. Kidd both of whom have graduated in medicine at McGill, and are members of the Osler Society of McGill. Miss Kidd is the first woman graduate to win the medal, and her paper on Dr. J. S. Helmcken of Victoria, B.C., will appear in the *Bulletin of the History of Medicine*. She has the rather unusual record of deciding to study medicine at the age of 36, whilst still carrying on her work as director of a group of chain stores in Vancouver. Her natural capacity for affairs was shown in her college career by her becoming editor of the *CAMSI Journal*, and also president of the Medical Women's Society. With this she combines a marked aptitude for medical writing.

Research Fellowships — The American College of Physicians.—The American College of Physicians announces that a limited number of Fellowships in Medicine will be available from July 1, 1948 to June 30, 1949. These Fellowships are designed to provide an opportunity for research training either in the basic medical sciences or in the application of these sciences to clinical investigation. Assurance must be provided that the applicant will be acceptable in the laboratory or clinic of his choice and that he will be provided with the facilities necessary for the proper pursuit of his work. The stipend will be from $2,200 to $3,000.

Application forms will be supplied on request to the American College of Physicians, 4200 Pine Street, Philadelphia 4, Pa., and must be submitted in duplicate not later than November 1, 1947. Announcement of the awards will be made as promptly as is possible.

The William Gibson Research Scholarship for Medical Women.—This Scholarship is awarded from time to time by the Society to qualified medical women who are subjects of the British Empire; and is tenable for a period of two years, but may in special circumstances be extended to a third year. The next award will be made in October, 1947.

In choosing a scholar the Society will be guided in its choice either by research work already done by her, or by research work which she contemplates. The scholar shall be free to travel at her own will for the purpose of the research she has undertaken. There is no competitive examination, nor need a thesis or other work for publication or otherwise, be submitted. Applications should be accompanied by a statement of professional training, degrees or diploma, and of appointments, together with a schedule of the proposed research. Applications must be accompanied by testimonials, one as to academical or professional status, and one as to general character. Envelopes containing applications, etc., should be marked on top left-hand corner "William Gibson Research Scholarship" and should be addressed to Mr. G. R. Edwards, Secretary, Royal Society of Medicine, 1, Wimpole Street, London, W.1, and be received not later than October 1, 1947.

The approximate value of the Scholarship will be £200 per annum.

It is announced that the Third American Congress of Obstetrics and Gynæcology will be held in St. Louis, Mo., September 8 to 12, 1947.

BOOKS RECEIVED

Control of Venereal Disease. R. A. Vonderlehr, Director, District No. 6, U.S. Public Health Service, and J. R. Heller, Chief, Venereal Disease Division, U.S. Public Health Service. 246 pp., illust. $2.75. Reynal and Hitchcock, New York, 1946.

Diseases of the Nervous System. F. M. R. Walshe, Physician in charge of the Neurological Department, University College Hospital, London. 351 pp., illust., 5th ed. $3.75. E. & S. Livingstone Ltd., Edinburgh; Macmillan Co. of Canada, Toronto, 1947.